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Workshop Manual for Radionuclide Handling and Radiopharmaceutical Quality Assurance

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Workshop Manual for Radionuclide Handling and Radiopharmaceutical Quality Assurance

Division of Training and Medical Applications

BRH
bureau of radiological health

WHO Collaborating Centers for:
- Standardization of Protection Against Nonionizing Radiations
- Training and General Tasks in Radiation Medicine
- Nuclear Medicine

This work was carried out under FDA Contract Number 223-76-6007

July 1982

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Bureau of Radiological Health
Rockville, Maryland 20857

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FOREWORD

The Bureau of Radiological Health develops and carries out a national program to control unnecessary human exposure to potentially hazardous ionizing and nonionizing radiations and to ensure the safe, efficacious use of such radiations. The Bureau publishes the results of its work in scientific journals and in its own technical reports.

These reports provide a mechanism for disseminating results of Bureau and contractor projects. They are distributed to Federal, State, and local governments; industry; hospitals; the medical profession; educators; researchers; libraries; professional and trade organizations; the press; and others. The reports are sold by the Government Printing Office and/or the National Technical Information Service.

The Bureau also makes its technical reports available to the World Health Organization. Under a memorandum of agreement between WHO and the Department of Health and Human Services, three WHO Collaborating Centers have been established within the Bureau of Radiological Health, FDA:

WHO Collaborating Center for Standardization of Protection Against Nonionizing Radiations;

WHO Collaborating Center for Training and General Tasks in Radiation Medicine; and

WHO Collaborating Center for Nuclear Medicine.

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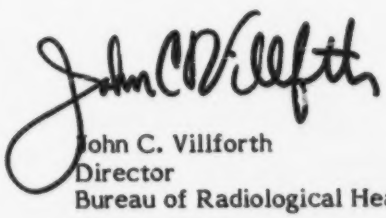


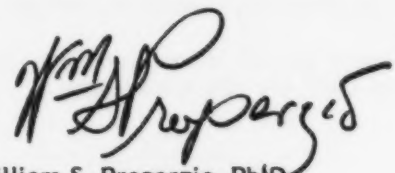
John C. Villforth
Director
Bureau of Radiological Health

PREFACE

This manual supplements the Radionuclide Handling and Radiopharmaceutical Quality Assurance Workshop. The workshop is designed to aid nuclear medicine technologists and other nuclear medicine personnel in organizing and implementing a radionuclide and radiopharmaceutical quality assurance program in their facility.

The manual covers operational characteristics and quality control testing of radionuclide generators, radionuclide calibrators, radiopharmaceutical drug products, radioactive gas administration, and fundamentals of radiation safety for the nuclear medicine facility. This information represents the collaborative efforts of the Division of Radiological Sciences of the University of Colorado Medical Center, the Radioisotope Laboratory of the University of Cincinnati Medical Center, and the Nuclear Medicine Laboratory, Bureau of Radiological Health, Food and Drug Administration, Cincinnati, Ohio. The University of Colorado performed their work under contract (FDA 223-76-6007) with the Bureau of Radiological Health. The contract was monitored by the Division of Radioactive Materials and Nuclear Medicine. Following an internal reorganization, these educational nuclear medicine activities were transferred to the Division of Training and Medical Applications.

We have produced this manual and the quality assurance workshop program to encourage nuclear medicine facility staff to adopt quality control procedures as a means of maintaining adequate performance levels. Comments and suggestions for changes in the manual will be welcomed as improvements occur in nuclear medicine practice.



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NOTE

The authors recognize that the currently used radiation units, roentgen, curie, and rad, are scheduled for obsolescence. To provide a common set of units for use in all branches of the physical sciences, the International Commission on Radiation Units and Measurements adopted, in 1960, the International System of Units (SI). In this System, the curie is replaced by the bequerel (1 Ci = 3.7×10^{10} Bq), the rad by the gray (1 rad = 0.01 gray), and the roentgen by coulomb per kilogram (1 roentgen = 2.58×10^{-4} coulombs per kilogram). Because the terms, roentgen, curie, and rad, are still in general use these units have been retained in this document. The conversion factors are given above for those who wish to make the conversion to SI units.

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ABSTRACT

Bureau of Radiological Health, FDA. Workshop Manual for Radionuclide Handling and Radiopharmaceutical Quality Assurance. HHS Publication FDA 82-8191 (July 1982) (52 pp.)

This manual is designed for use in the Radionuclide Handling and Radiopharmaceutical Quality Assurance Workshop which aids nuclear medicine technologists and other nuclear medicine personnel in organizing and implementing quality assurance programs in their facility. The manual was developed collaboratively with the Universities of Colorado (Contract FDA 223-766007) and Cincinnati Medical Centers and the Nuclear Medicine Laboratory, BRH, FDA. The six sections include material on generator operation, yield, contaminants, and assay; calibrator testing procedure; radiopharmaceutical sterility, pyrogenicity, and purity; Xenon storing, handling, and disposal; and safety for patient and personnel: shielding, monitoring, decontamination, and good working habits.

SECTION I

QUALITY ASSURANCE AND RADIATION PROTECTION: CORNERSTONES OF GOOD NUCLEAR MEDICINE

Nuclear medicine, over the last quarter century, has evolved from detection of radioactive iodine in the thyroid to analysis and display of the movement and distribution of a large number of radiopharmaceuticals in a variety of organ systems in the body. This evolution of nuclear medicine has been possible because of progress in the production of radionuclides, radiopharmaceuticals, and nuclear medicine instrumentation. In spite of these advances and improvements, variances in radiopharmaceutical products and instrument operation occur in the day-to-day practice of nuclear medicine. To detect these changes and to determine whether they are outside the limit of acceptability, a performance monitoring program should be maintained in every nuclear medicine facility. This ongoing radiopharmaceutical and nuclear instrumentation performance verification is commonly referred to as quality assurance.

Various advisory and regulatory agencies have recognized the importance of quality assurance in nuclear medicine. These agencies require the performance of testing procedures on a regular basis for accreditation and licensure of nuclear medicine services. As an example, the Joint Commission on Accreditation of Hospitals (JCAH) has published the following standard for hospital nuclear medicine services: "Standard III - Nuclear medicine activities shall be governed by quality control policies and procedures that ensure diagnostic and therapeutic reliability and safety of patients and personnel" (1). The JCAH interpretation of this standard is: "All radioactive materials, reagents, and standards shall be prepared, stored, and checked at a defined interval to be determined by the director, to ensure accuracy, patient safety, and precision of results. All reagents must be labeled to indicate identity, date of preparation, and assay. Instrument calibration procedures sufficient to affirm proper performance shall be conducted each day the instrument is used, and the results recorded." Licensure standards of the U.S. Public Health Service for clinical laboratories require that: "Quality controls imposed and practiced by the laboratory must provide for and ensure preventive maintenance, periodic inspection and testing for proper operation of equipment and instruments; validation of methods, evaluation of reagents and volumetric equipment, surveillance of results; and remedial action to be taken in response to detected defects" (2). Regulations of the Social Security Administration covering services of independent laboratories under the Health Insurance for the Aged program have been amended to require adherence to the PHS Clinical Laboratory Licensure standards (3).

In addition to standards that address patient safety, there are other standards that are directed to the overall safe handling of radioactive materials. These standards are more rigorously administered on an individual user basis by licensure requirements of the Nuclear Regulatory Commission (NRC) or, in the case of agreement States, by a designated State agency.

Ultimately the success of any program designed to ensure a consistent level of performance and safety depends upon the commitment of the people involved to perform quality assurance test procedures routinely, to record the results systematically, and to review the results frequently. If these objectives are realized, patient services will be

improved and unnecessary radiation exposure, inaccurate diagnostic information, and needless repetition of studies will be reduced.

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2. Clinical Laboratories Improvement Act of 1967, Code of Federal Regulations, Title 42, Part 74. Public Health Service, U.S. Department of Health and Human Services, Washington, D.C. (1968).

3. Conditions for Coverage of Services of Independent Laboratories. Code of Federal Regulations, Title 10, Part 405, Subpart M. Social Security Administration, U.S. Department of Health and Human Services, Washington, D.C. (1974).

SECTION II

RADIONUCLIDE GENERATORS

In recent years radionuclide generators have become the principal source of short-lived radionuclides for the nuclear medicine laboratory. In a radionuclide generator, the parent radionuclide is usually a reactor or cyclotron (accelerator) produced nuclide that decays to a different radionuclide or "daughter". Numerous potentially useful generator systems have been identified (1,2). However, a number of conditions must be met if the generator is to be clinically useful. The parent must be a relatively long-lived nuclide which decays to a short-lived daughter which can be easily separated from the parent at regular intervals. The daughter radionuclide must emit gamma radiation of a useful energy (80-400 keV) with minimum particulate radiations, should decay to a stable or long-lived nuclide, and must be easily incorporated into a variety of radiopharmaceuticals. Only one generator that meets all these requirements, the very important ^{99}Mo-^{99m}Tc type, is currently commercially available. An ^{81}Rb-^{81m}Kr generator is also available. The inert gas with a 13-second half-life is used for ventilation studies. Other generators, such as ^{87}Y-^{87m}Sr, ^{68}Ge-^{68}Ga, and ^{113}Sn-^{113m}In, are feasible but have been shown to be less useful. Strontium-87^m was used for the detection of bone tumors. Strontium-87^m was replaced by ^{18}F and then by the ^{99m}Tc labeled bone imaging agents. The ^{68}Ga generator and ^{68}Ga labeled agents for bone scanning have not been used to any great extent since the introduction of ^{99m}Tc. This generator could be useful in the future because of the nearly ideal half-lives of the daughter (^{68}Ga, T½ 68 min) and the parent (^{68}Ge, T½ 275 days), and the high radionuclide purity of ^{68}Ga, depending on the progress made in imaging 511 keV annihilation photons and the development of useful radiopharmaceutical agents labeled with ^{68}Ga. The ^{113}Sn - ^{113m}In generator was used in remote locations, where weekly deliveries of ^{99m}Tc generators were impossible. In 1982, only a few remote foreign laboratories use ^{113m}In and ^{113m}In labeled radiopharmaceuticals. The ^{99m}Tc and ^{81m}Kr generators have been approved by the Food and Drug Administration (FDA) for routine commercial distribution as NDA radiopharmaceuticals.

The physical and chemical characteristics of the ^{99}Mo-^{99m}Tc generator make it valuable in nuclear medicine laboratories. Molybdenum-99 decays with a half life of 66.7 hrs to ^{99m}Tc and ultimately to ^{99}Tc. As shown in the decay scheme in Figure 1, approximately 87 percent of all disintegrations of ^{99}Mo yield the metastable state ^{99m}Tc. In the remainder of disintegrations ^{99}Mo decays directly to ^{99}Tc by β-emission with the immediate release of several photons. The photons include a number of high energy gamma rays, the most prominent of which have energies of 740 keV and 780 keV. Technetium-99m with a physical half-life of 6 hours, decays by isomeric transition to ^{99}Tc. In 12 percent of these decays an internal conversion electron is ejected, and in 88 percent of the isomeric transitions a γ-ray of 140 keV is emitted. Thus, ^{99m}Tc provides a high yield of photons suitable for imaging. Technetium-99 also is radioactive and decays with a half-life of 2.1 x 10^5 years to stable ^{99}Ru (3).

Technetium 99m may be separated from the parent ^{99}Mo by sublimation techniques, solvent extraction or by the use of a generator based on column chromatography. With the solvent extraction technique, the ^{99m}Tc is extracted with methyl ethyl ketone, which is then evaporated in a water bath to leave solid sodium pertechnetate. This is then redissolved in physiological saline and sterilized. Sublimation techniques have not proven economically feasible. The use of a generator based on chromatographic separation is, however, much simpler for general availability of ^{99m}Tc.

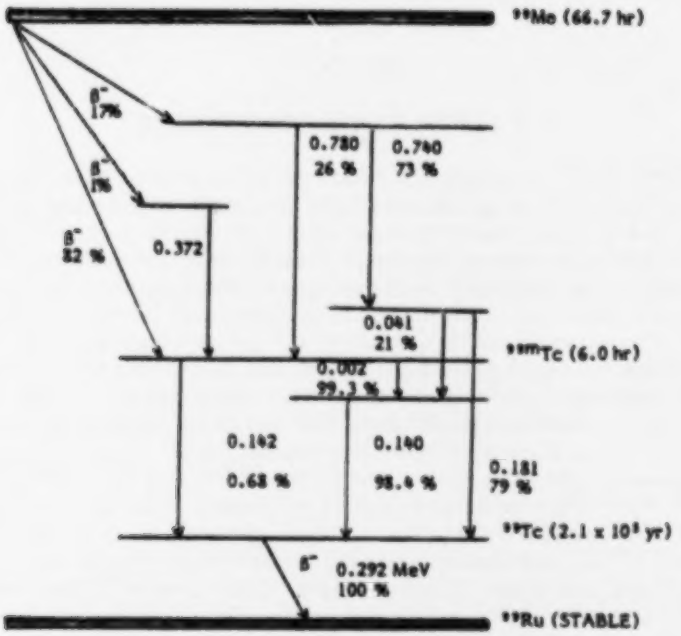


Figure 1. Decay scheme of ^{99}Mo.

GENERATOR OPERATION

In a radionuclide generator, the clinically used daughter can be separated from the parent because of differences in the chemical and physical properties of parent and daughter. A simplified ^{99m}Tc generator is shown in Figure 2. The parent is absorbed on an aluminum oxide (alumina) column. When a reagent in which the daughter is soluble is passed over the column, the daughter is washed out in the eluate. Examples of reagents (eluents) include physiologic saline for ^{99}Mo-^{99m}Tc generators and dilute hydrochloric acid for a ^{113}Sn-^{113m}In system. The daughter radionuclide in the eluate solution is collected in sterile vials which are shielded to reduce exposure to nuclear medicine personnel. If the manufacturer's recommendations are followed, commercial generators usually provide adequate shielding for the parent and daughter radionuclides and a quick, efficient, sterile system for collecting the eluate.

Molybdenum-99 for use in a radionuclide generator is obtained from two sources. Neutron bombardment of ^{98}Mo in a reactor ((n,γ) reaction) produces ^{99}Mo of acceptable specific activity. Molybdenum-99 of high specific activity with no carrier added also may be obtained as a product of the fission of ^{235}U. The molybdenum in the form of molybdate ion ($MoO_4^{=}$) is loaded on an aluminum oxide (alumina) column. The amount of alumina needed to hold the molybdenum is a function of the specific activity of the molybdenum. Because of its lower specific activity, reactor-produced ^{99}Mo contains more stable molybdenum, and hence requires more alumina for binding, to produce a generator of a specified activity. After loading, the column is washed with sterile saline to remove unbound ^{99}Mo. Sterilization of the generator is usually accomplished by terminal autoclaving of the column or by use of an in-line bacteriological filter placed between the column and the eluate collection vial. The generator is then eluted and the (TcO_4^-) eluate tested for yield of ^{99m}Tc, sterility, apyrogenicity, pH, Al^{+++} breakthrough, ^{99}Mo breakthrough, clarity, radionuclide purity and radiochemical purity. The daughter, ^{99m}Tc, is present on the column as pertechnetate (TcO_4^-) and is eluted in the chemical form sodium pertechnetate ($NaTcO_4$) since 0.9 percent sodium chloride (saline) is used as an eluent. Sodium pertechnetate obtained from the generator can be used directly for several studies

including brain imaging and thyroid studies. Many additional radiopharmaceutical compounds can be prepared by reduction of the ^{99m}Tc-pertechnetate from the Tc(+7) state to a lower oxidation state of Tc(+4).

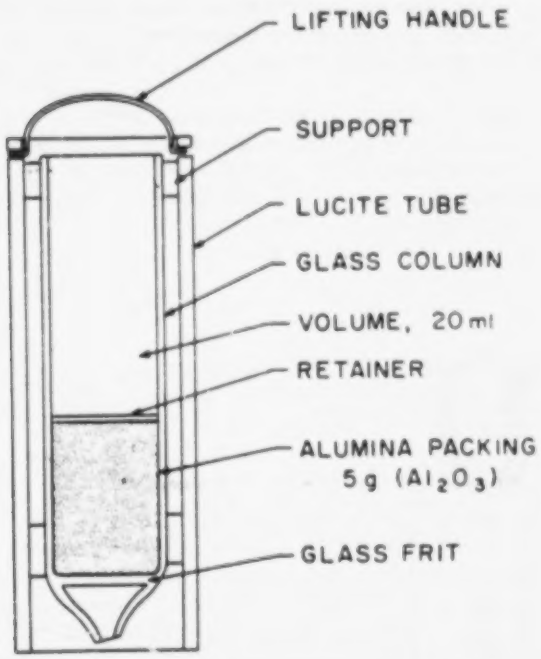


Figure 2. Diagram of simplified ^{99m}Tc generator.

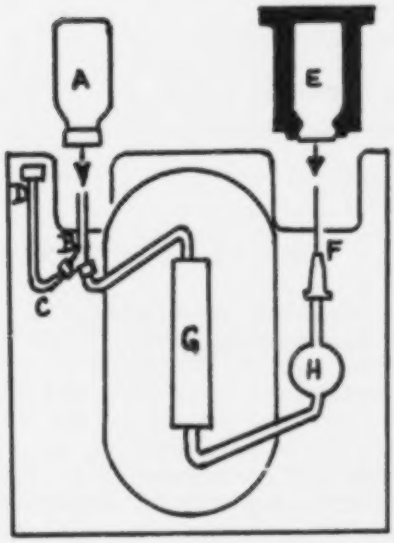
Commercial ^{99}Mo- ^{99m}Tc Generators

There are a few variations in ^{99}Mo-^{99m}Tc generators available commercially. Both reactor and, more recently, fission moly generators are readily available. The functional difference in these two types of generators is the amount of saline necessary for elution. A reactor-produced generator requires 15-25 ml of saline for complete elution, whereas a fission moly generator requires only 4-8 ml per elution because of the higher specific activity of molybdenum and the smaller column size of the latter. Hence, the fission moly generator yields a higher concentration (mCi/ml) of ^{99m}Tc for a given quantity of activity on the column. For an even higher concentration, either generator may be eluted fractionally, with 1 out of 3 or 4 elution vials yielding the highest concentration of ^{99m}Tc activity. With some very large generators, the eluate may be diluted with saline to reduce the concentration to useful levels.

The method of elution of technetium also varies in commercial generators. One type of generator has a dry column, represented schematically in Figure 3. After elution with physiologic saline, air continues to flow through the generator essentially drying the column. If the column were left wet, the next elution would produce only a fraction of the expected activity because of a change in column pH caused by radiolysis of the residual water. A second type of generator has a wet column with a large amount of self-contained saline that is permanently connected to the column by a tube. The path of the saline flow is continuous from the saline bottle to the collection point, keeping the column wet at all times. This procedure alleviates the need to dry the column. To prevent buildup of oxidizing agents in the column caused by radiolysis of water, wet column generators must be eluted every day, especially on the day of receipt of the generator. Also, if air bubbles become trapped in the

column, the generator may elute only very slowly if at all. Another problem is the possibility that the wet column may freeze and crack if left for any length of time on a cold loading dock. A wipe test of the generator may detect this problem although the packaging often will prevent spread of contamination. If freezing is suspected and the generator will not elute, put it in a safe storage area and request a replacement generator. When dry columns are allowed to become very cold, the saline eluant freezes and will not elute the ^{99m}Tc. However, the columns may be thawed by warming gently with a heat lamp. These problems very rarely occur with any generator; however, if they do occur, good radiation safety practices are required to minimize exposure and possible contamination.

The manufacturer's directions should be followed when a generator is eluted. In particular, sterile techniques must be used throughout the procedure. To maintain sterility, the eluant and collection ports must be protected when not in use. All manufacturers of generators provide vial shields to contain the eluate vial. These shields should always be used to reduce personnel exposure.



A charge vial (A) containing 0.9% sodium chloride injection solution is placed onto the double needle (B), vented through tube (C) fitted with a cotton pledget filter (D). Elution begins automatically when a shielded evacuated collection vial (E) is placed onto needle (F). As the saline is removed from charge vial (A) it passes through shielded column (G) loaded with the parent ^{99}Mo. ^{99m}Tc is eluted and the eluate then passes through filter (H) into shielded collection vial (E).

Figure 3. Diagram of dry column generator.

GENERATOR YIELD

A radionuclide generator is potentially available whenever there is a relationship between two radioactive nuclides in which the parent half-life is substantially longer than the half-life of the daughter. As the parent decays to the daughter, the production of daughter atoms exceeds the decay of daughter atoms until an equilibrium is reached where the number being produced and decaying are equal. Beyond this equilibrium point, the daughter decays with an apparent half-life equal to the half-life of the parent (transient equilibrium). Figure 4 illustrates the parent-daughter activity relationship, with the first elution of ^{99m}Tc occurring at 24 hours, a typical situation in a clinical nuclear medicine department. Because only 86 percent of ^{99}Mo disintegrations yield ^{99m}Tc, the activity of ^{99m}Tc never exceeds the activity of ^{99}Mo. Following elution, the activity of the daughter again increases. If additional ^{99m}Tc is needed, the generator may be eluted again a few hours following the first elution, as shown in Figure 4.

Table 1 illustrates the percentage yields obtainable at one hour intervals following previous elution of a ^{99m}Tc generator. This table is useful in estimating yields if a generator must be eluted more than once in a 24-hour period. For example, if 400 mCi were obtained from an 8 a.m. elution, a second elution at 1 p.m. (5 hours elapsed) would be expected to yield 400 mCi x 0.362 or 145 mCi. The percentage yield increases rapidly initially and approaches its maximum value approximately 12 hours following elution, with the yield increasing rather slowly after that time.

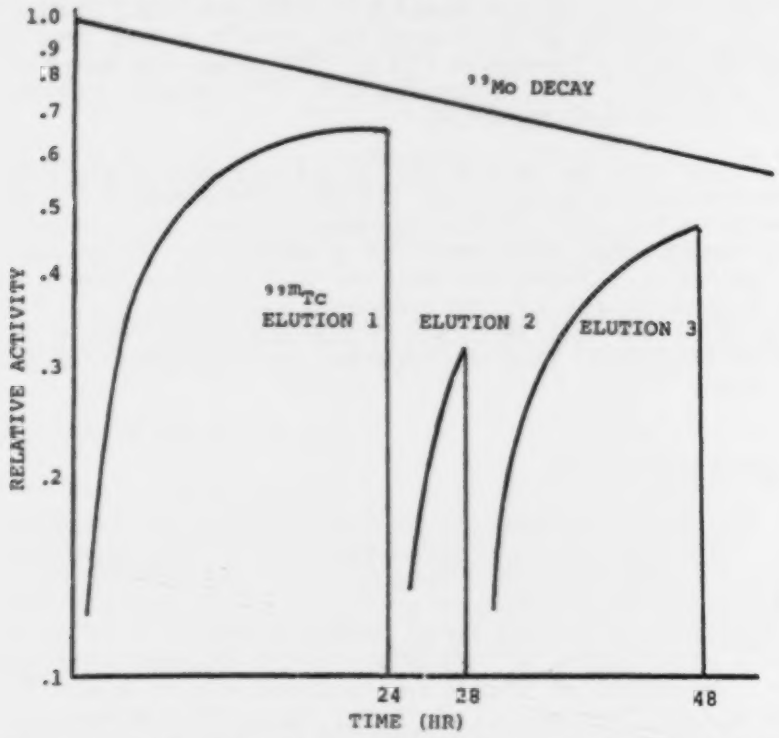


Figure 4. Parent-daughter relationship in a typical ^{99}Mo-^{99m}Tc generator system.

Table 1. Expected yield of ^{99m}Tc after prior elution

Elapsed time (hr)	Fraction of activity of previous elution	Elapsed time (hr)	Fraction of activity of previous elution
0.5	0.0475	12	0.5921
1	0.0921	13	0.6092
2	0.1731	14	0.6236
3	0.2446	15	0.6358
4	0.3073	16	0.6457
5	0.3624	17	0.6638
6	0.4105	18	0.6601
7	0.4525	19	0.6650
8	0.4891	20	0.6685
9	0.5209	21	0.6709
10	0.5483	22	0.6723
11	0.5719	23	0.6728
		24	0.6725

ELUATE CONTAMINANTS

The ^{99m}Tc eluate is essentially the same from any of the generators mentioned; however, generators may yield a number of possible contaminants. The two contaminants of major concern result from breakthrough of ^{99}Mo and Aluminum ion (Al^{+3}). Other possible contaminants of reactor ^{99}Mo-^{99m}Tc generators include ^{134}Cs, ^{86}Rb, ^{60}Co, ^{124}Sb and ^{95}Zr (4). Fission moly generators may also possess a number of contaminants, particularly ^{131}I and ^{132}I. With the exception of ^{132}I, all contaminants have been detected in levels below U.S. Nuclear Regulatory Commission (NRC) limits of 0.15 µCi per mCi ^{99m}Tc (5-8). Iodine-132 has on occasion been found to exceed these limits (5,7) and methods of determining the presence of ^{132}I in ^{99m}Tc eluate are described in the literature (6). The presence of alpha contamination in ^{99m}Tc eluates produced from fission molybdenum has also been investigated (8).

Limits of 1 µCi ^{99}Mo per mCi of ^{99m}Tc, not to exceed 5 µCi ^{99}Mo per patient dosage, have been established by NRC (5-8). This limit is referenced in licenses for radionuclide use issued by the NRC and most state licensing agencies. The Food and Drug Administration (FDA) requires that users follow all guidelines set by the manufacturers of radionuclide generators, including the limit on ^{99}Mo contamination in ^{99m}Tc eluate. United States Pharmacopeia (U.S.P.) has established a limit of 0.15 µCi ^{99}Mo/mCi^{99m}Tc Molybdenum contamination could be caused by migration of the ^{99}Mo in the alumina column with successive elutions. Thus, it is important that testing for ^{99}Mo breakthrough be performed routinely.

ASSAY FOR MOLYBDENUM-99

There are two common methods for assaying the amount of ^{99}Mo present in ^{99m}Tc eluate. Most radionuclide calibrators are equipped with a "Moly shield", with which it is possible to check the eluate by following the directions of the calibrator manufacturer. The thickness of the lead shield is sufficient to attenuate almost all of the ^{99m}Tc photons, with only partial attenuation of the high energy photons emitted from ^{99}Mo. The calibrator provides either a direct reading of ^{99}Mo or the reading obtained is multiplied by a correction factor. The activity of ^{99}Mo is then compared with the total ^{99m}Tc activity to determine the µCi of ^{99}Mo per mCi of ^{99m}Tc. Since ^{99}Mo decays more slowly than ^{99m}Tc it is also necessary to calculate the time at which the critical limit for ^{99}Mo contamination would be exceeded particularly if the level of contamination approaches the maximum permissible concentration at the time of measurement.

A method commonly used to determine the degree of ^{99}Mo contamination in ^{99m}Tc eluate is to use a ^{137}Cs standard, called a "Mock-Moly" standard. Since the response of the scintillation detector is similar for ^{137}Cs (662 keV) and ^{99}Mo (primarily 740 and 780 keV), the activity of ^{99}Mo may be determined by comparison with the known activity of the ^{137}Cs standard. The basic procedure is:

1. Calibrate the probe or well scintillation counter with the ^{137}Cs standard using a 652-672 keV window.
2. Set a window of 600-900 keV to count the two sources.
3. Determine background for the 600-900 keV window.
4. Count the eluate for a set time in a lead shield with a thickness equal to that of the cesium source shield (~4 mm).
5. Count the ^{137}Cs standard in its shield.

6. After subtracting background determine the activity of ^{99}Mo using the formula:

$$\mu Ci\ ^{99}Mo = \frac{(\mu Ci\ ^{137}Cs\ standard)\ x\ (net\ cpm\ eluate)}{(net\ cpm\ ^{137}Cs\ standard)} \times 4.5$$

The 4.5 correction factor is due to the difference in fractional emission of gamma rays from the two radionuclides. Molybdenum-99 emits a variety of gamma rays with energies greater than 600 keV in 18.7 percent of all disintegrations, while ^{137}Cs decays to the metastable state of ^{137}Ba which then emits a 662 keV gamma ray in 84.5 percent of all ^{137}Cs disintegrations. Thus, a correction factor of .845/.187 = 4.5 must be used. Some "Mock-Moly" standards state the activity of ^{137}Cs as "^{99}Mo equivalent." With these standards the correction factor is included in the stated activity and should not be used in the calculation.

7. Divide the result in (6) by the total number of mCi of ^{99m}Tc in the eluate as determined with the calibrator, as follows:

$$\text{Molybdenum-99 Breakthrough} = \frac{^{99}Mo\ \mu Ci}{^{99m}Tc\ mCi}$$

8. If the level of contamination is close to the maximum permissible concentration, determine the time at which the acceptable limit is exceeded as described above.

ASSAY FOR ALUMINUM ION (Al^{+3})

Aluminum ion from the generator column may contaminate the eluate. If a significant amount of aluminum ion is present, it may react with phosphate buffers in colloid kit preparations to form an aluminum phosphate precipitate that coprecipitates the colloid. Significant amounts of aluminum contamination also may cause agglutination of red blood cells, resulting in lung trapping of micro-emboli in the patient. Present limits of aluminum ion contamination for ^{99m}Tc eluates are 20 µg per ml for neutron activated generators and 10 µg per ml for fission generators. These limits are provided by the United States Pharmacopeia (9).

A simple test kit is available commercially* for testing aluminum ion concentration. The kit contains a specially impregnated paper and a standard solution of aluminum ion solution (15 µg/ml). A drop of ^{99m}Tc eluate can be checked for aluminum ion contamination using the colorimetric procedure described in the instruction book for the procedure. If a positive test is observed, the eluate should not be used.

A chemical contaminant, which acts as an oxidant, is associated with solutions of ^{99m}Tc obtained from generators. Trace levels of the oxidant, due mostly to hydrogen peroxide, occur on generator columns by the interaction of the high radiation field with water left on the column. This is most significant when the generator has not been used for several days (e.g., a generator just delivered). The minute quantities of peroxide are not toxic, but they may cause poor tagging in the preparation of kit radiopharmaceuticals and electrolytic stannous ion labeling of ^{99m}Tc albumin. The peroxide competes with Tc(+7) for the reducing agents (e.g., stannous ion) and prevents adequate reduction of pertechnetate to Tc(+4) or Tc(+5). There is little need to check routinely for this contaminant since it occurs only rarely.

If the generator has not been eluted for several days, relatively large amounts of ^{99}Tc will be present in the ^{99m}Tc eluate (10). If poor tagging occurs, particularly on the first day the generator is eluted, minute quantities of peroxide or large amounts may be the cause.

*New England Nuclear Corporation, 601 Treble Cove Road, North Billerica, Massachusetts 01862.

It is important to use only those eluting solutions that are supplied with the $^{99}Mo/^{99m}Tc$ generator system by the manufacturer. The use of other than specified eluting solutions may cause improper eluting of the generator and ultimately a poor quality radiopharmaceutical. Eluents containing preservatives have also been identified as causes of poor tagging in prepared radiopharmaceutical kits.

TIN-113 - INDIUM-113^{m} GENERATOR

Another generator used in some nuclear medicine laboratories is ^{113}Sn-^{113m}In. The daughter ^{113m}In has a half-life of 100 minutes and decays by isomeric transition to stable ^{113}In with the emission of 392 keV gamma ray. Although no particles are emitted from the nucleus during decay of ^{113m}In, internal conversion electrons are emitted in 38 percent of the disintegrations. These conversion electrons contribute to the radiation dose. The parent ^{113}Sn has a half-life of 115 days, allowing the generator to be used for a long period of time (up to 6 months). Indium-113^{m}, either in the ionic form of $^{113m}InCl_3$ or incorporated into radiopharmaceuticals, has been used in a variety of applications, including brain, blood pool, placental, and kidney imaging.

The basic generator design is similar to that described previously, for the ^{99}Mo-^{99m}Tc generator with the ^{113}Sn loaded on a column of hydrous zirconium oxide. The ^{113m}In is eluted with 0.05 N hydrochloric acid (HCl) and assayed by comparison to a precalibrated standard of ^{113}Sn in transient equilibrium with ^{113m}In.

Possible contaminants of the ^{113m}In eluate include ^{113}Sn, Zr, and stable Sn. Contamination by ^{113}Sn may be tested by eluting the generator for ten days prior to use, allowing the eluate from each elution to decay for 48 hours. The eluate is then tested for the presence of ^{113m}In (2). Because the eluted ^{113m}In will have decayed, any ^{113m}In present is due to the decay of ^{113}Sn in the eluate. The levels of ^{113}Sn in the eluate must not exceed 0.2 μCi per mCi of ^{113m}In. Chemical contaminants may be evaluated by colorimetric tests described in the literature (11). The eluate should also be tested for sterility on receipt of the generator and on a routine basis thereafter. The generator should be used following the manufacturer's instructions, and should not be used beyond the expiration date of six months after calibration.

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SECTION III

QUALITY ASSURANCE OF RADIONUCLIDE CALIBRATORS

Radionuclide calibrators are used in nuclear medicine departments to assay the activity of radiopharmaceuticals to be administered to patients. In some cases, radiopharmaceuticals are delivered precalibrated by the commercial supplier or a radiopharmacy. In other cases, radiopharmaceuticals are prepared on site, usually with the eluate from a radionuclide generator. In either situation, the activity of radiopharmaceuticals should be assayed prior to administration, because responsibility for the accuracy of the administered activity, and the concomitant estimate of radiation dose to the patient, rests with the persons administering the radiopharmaceuticals. Hence, it is essential that the radioactivity measurements of radiopharmaceuticals by radionuclide calibrators be accurate.

In most nuclear medicine departments, well ionization chamber radionuclide calibrators are preferred for routine use because they provide a wide range of activity measurements and exhibit reasonable stability of performance from day to day. Additionally, well ionization chamber calibrators are easy to use and their readings easy to interpret. The basic electrical design of a calibrator includes an ionization chamber coupled to a current-to-voltage converter, a range selector, a nuclide correction circuit, and a readout device as shown in Figure 5.

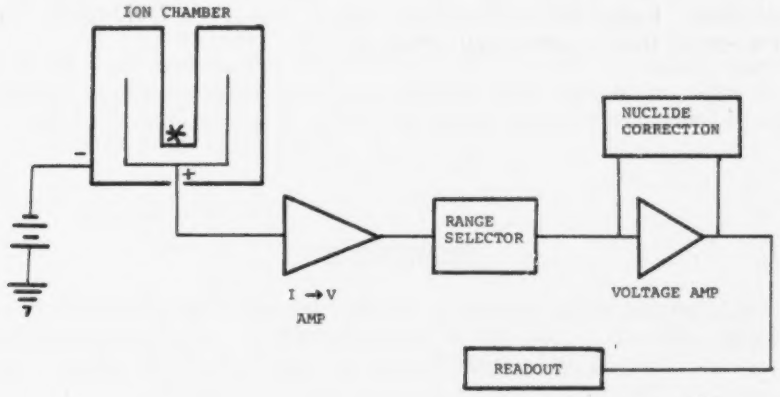

Figure 5. Block diagram of a radionuclide calibrator (8).

The ionization chamber is a sealed, gas-filled (e.g. argon) double-walled chamber containing a pair of electrodes kept at a high potential difference. When a radioactive source is lowered into the well of the chamber, radiation ionizes the gas within the chamber, thereby releasing electrons which are collected at the positive electrode. These electrons constitute an electrical current which is proportional to the activity of the radioactive source placed in the well. The current is sensed by an electrometer (I→V converter) that develops an output voltage proportional to the input current. The type of electrometer shown in Figure 5 operates by developing a feedback current that cancels or nulls the ionization chamber current at the input of the electrometer. The range selector on the calibrator optimizes the feedback resistance of the electrometer for accuracy and response time to the appropriate scale (e.g. millicuries or microcuries) of the readout device. Other electrometer designs may not use a feedback resistance, but the range selection

will involve switching large precision resistances. The nuclide correction setting adjusts the amplification of the output voltage so that the activity reading of the readout device will be correct for the particular radionuclide. The second correction is necessary because the current produced in the ion chamber is proportional to both the energy and the fractional emission of photons from the radionuclide. The nuclide correction usually is accomplished in one of two ways. Some calibrators have a fixed resistance for each radionuclide which is introduced into the circuit by a plug-in module or an individual setting on the calibrator console. Other calibrators use a variable resistor (potentiometer), and the resistance which is introduced into the circuit is determined by setting the variable resistor dial at a specified number.

Most ionization chambers are sensitive to thermal, mechanical, and electronic shock. Hence, care must be taken to ensure that the calibrator is not moved or jarred after it has been installed. Also, the calibrator should not be turned off or exposed to rapid fluctuations in temperature. If these influences do occur, quality assurance tests should be implemented immediately to ensure that the calibrator is operating properly. To ensure the most reliable performance, the calibrator should be kept in a clean, dry environment at constant temperature.

QUALITY ASSURANCE TESTING

A quality assurance program for radionuclide calibrators consists of two parts. The first part is to determine that the instrument is responding accurately; the second part is to ensure that this response is constant on a day-to-day basis. The accuracy of the calibrator response is determined by comparing the activity measured with the calibrator to the known activity of a standardized source. The accuracy of assay may be influenced by factors such as the geometry dependence related to the type of container used to hold the radioactive sample and its position within the well; variations in background; presence of impurities; or a nonlinear response across the range of activities to be assayed in the calibrator. Once accuracy has been determined and appropriate measures have been taken to calibrate the radionuclide calibrator, it may be monitored by daily precision testing with a long-lived standard. These tests are discussed below in detail.

Test for Accuracy

An assessment of assay accuracy can be made with clinically applicable standards. These standards are obtainable from the National Bureau of Standards, or from a number of manufacturers. In addition, standard samples of ^{131}I and ^{99m}Tc may be prepared using the method described by Hare, et. al (1). The preferred method for calibration has been stated recently in a standard adopted by the American National Standards Institute (ANSI) (2). Recommended calibration practices in this standard include the following statements:

> "Initial Calibrations. Instruments shall be calibrated with identified radionuclide sources of known activity and established purity. . . . calibrations should be performed with standard sources of each radionuclide of interest, if at all feasible."
>
> "Activity Ranges. Calibration of the equipment should cover as completely as practicable the activity range for which it will be used, particularly those ranges of activity of radionuclides to be administered to patients. . . ."
>
> "Energy Range. Calibration shall be performed over the energy range of proposed application."

Thus, calibration of ^{99m}Tc would best be performed with a standardized source of ^{99m}Tc. The container used to hold the sample and its position within the well must also be considered. For example, corrections must be made when assaying a plastic syringe at a location a few centimeters above the bottom of the well, if the calibrator was calibrated

with a glass ampule at the bottom of the well. Where short-lived standards are not readily available, an alternate method may be used that involves comparison of the radionuclide of interest with a long-lived standard of similar energy (3). For example, a standard source of ^{57}Co may be used to calibrate the ^{99m}Tc setting. Although the energies of the two radionuclides are similar, the fractional emissions are different, and the reading for ^{57}Co at the ^{99m}Tc setting will not be correct. In calibrating the ^{99m}Tc setting, appropriate corrections must be made to account for this effect. If the radionuclide calibrator is not responding within ±5 percent accuracy, either each observed reading may be multiplied by an appropriate correction factor, or the resistance in the nuclide correction module may be adjusted to yield the correct reading. The method of correction used generally is determined by the model of the radionuclide calibrator and the ease with which changes in the nuclide correction module may be made.

Studies of the accuracy of well ionization type calibrators indicate the need for periodic calibration (1,4,5). In these studies, radionuclide calibrators frequently were inaccurate by 10 percent, and occasionally by as much as 25 percent. Yearly calibration, with recalibration after major servicing of the instrument, should be sufficient to ensure accuracy (2,6)

Tests for Geometry and Linearity

Factors such as geometry and linearity may influence the accuracy of readings obtained with a radionuclide calibrator. These factors should be determined during initial testing or after major repair, and linearity should be evaluated quarterly thereafter (6). Geometry effects are of two types. First, the size, shape, and material of the container for the radioactive sample may influence the measurement of activity. This influence may be a significant factor particularly for low-energy radionuclides such as ^{125}I and ^{133}Xe, where both self-attenuation and attenuation by the container may be substantial (7). The position of the sample within the well of the ionization chamber may also affect the reading. Figure 6 illustrates the response of three different calibrators to the same activity at various vertical positions within the well. The response varies by as much as 15 percent. This effect must be considered in calibration of an instrument, so that appropriate corrections can be applied if the position of the samples commonly assayed is different from that for the standards used.

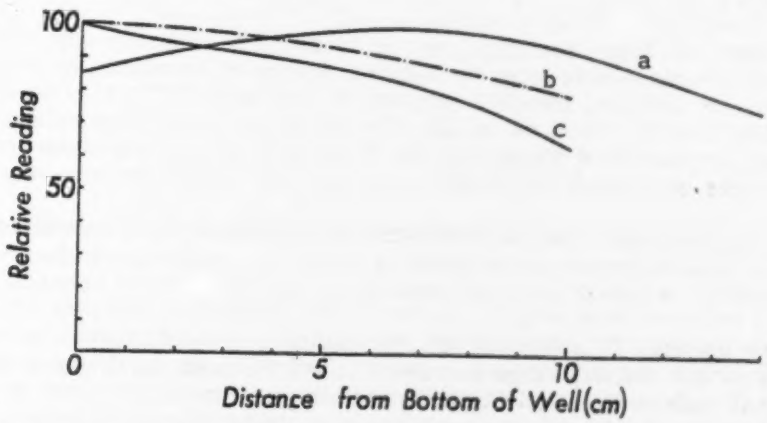

Figure 6. Relative response of ionization chamber calibrators of three different manufacturers (a,b,c) to ^{99m}Tc samples as a function of sample position.

The response of a calibrator may also be dependent on the amount of radioactivity assayed. Ideally, the calibrator will respond linearly over a range of activities from a few microcuries to several curies. However, there is sometimes an inaccurate response in the

high millicurie range, where the reading may be lower than the true activity. Due to saturation effects, some calibrators may be subject to nonlinearities above the range of 700 - 800 mCi (8). A knowledge of this dependence is necessary if high activity samples (e.g., eluate from a generator) are to be assayed accurately. Protocols for determining these factors are provided at the end of this section.

Test for Precision

The second portion of a quality control program involves the routine monitoring of the operational consistency of a calibrator. This monitoring ensures that the calibrator is operating in the same manner day by day, and that the original calibration of accuracy is still valid. The ANSI report recommends:

> "Reference Source Checks. Calibration checks using at least one long-lived reference source (e.g., ^{137}Cs) shall be performed and logged on each work shift during which the instrument is used . . ." (2).

Long-lived sources in the range of photon energies and activities of interest are preferred for this type of testing. Typical sources include ^{137}Cs (100-200 μCi) and ^{57}Co (2-5 mCi) which furnish photons in the energy range of ^{99}Mo and ^{99m}Tc, respectively, as shown in Table 2. These sources provide a check of the reproducibility of readings for different ranges and photon energies. They may also be used to check the readings obtained at settings for other radionuclides (e.g. ^{131}I, ^{133}Xe, ^{67}Ga). A protocol for routine testing of a calibrator is provided at the end of this section.

Table 2. Sources for radionuclide calibrator quality assurance

Source nuclide	$T_{½}$ and principal photon energies	Simulated nuclide	$T_{½}$ and principal photon energies	Form	Nominal activity
^{57}Co	270 days 122 keV 136 keV	^{99m}Tc	6 hours 140 keV	vial (gel)	2-5 mCi
^{137}Cs	30 years 662 keV	^{99}Mo	67 hours 740 keV 780 keV	vial (gel)	100-200 μCi

Sources must be of high radionuclidic purity, so that contaminants do not introduce error over a long term of calibrator checking. This requirement is especially important for ^{57}Co which sometimes has a significant amount of ^{60}Co contamination. Sources should be obtained in an evaporated or gel form to prevent spread of contamination if broken. Wipe tests performed on receipt of the source will ensure that the vial is not contaminated externally.

The objective of daily quality assurance testing is to determine if a calibrator responds consistently from one day to the next (a correction for decay may be taken into account). The primary objective is to measure reproducibility rather than accuracy of assay of the long-lived source.

Radionuclide calibrators are instruments that require regular checks and correct usage to ensure accurate operation. As with any instrument, knowledge of how a calibrator works helps to ensure its most accurate and efficient use. If the tests outlined here are performed as indicated, a calibrator can be used with confidence to obtain correct assays of the activity of radiopharmaceuticals prior to administration.

RADIONUCLIDE CALIBRATOR QUALITY ASSURANCE PROCEDURE

Introduction

The following protocol describes a method for using ^{57}Co and ^{137}Cs sources for checking ^{99m}Tc and ^{99}Mo settings of a radionuclide calibrator to test the response stability of two settings of the calibrator. The emission energies of these sources come closest to simulating appropriate clinical conditions. However, other long-lived sources of appropriate activity may also be used.

Precision Testing

1. Adjust the radionuclide selector dial to the setting for ^{99m}Tc.
2. Adjust the background control until a reading of zero is obtained. If this is impossible, the background reading must be recorded and subtracted from all subsequent readings.
3. Insert a ^{57}Co source (approximately 2-5 mCi will best simulate clinical activities).
4. Allow sufficient time (at least several seconds) for the instrument to stabilize.
5. Record the reading shown on the meter minus the background reading (step 2 above) in the log book, and plot the net reading on a graph. (Note that the reading of ^{57}Co for the ^{99m}Tc calibration setting will not yield the correct amount of activity for the ^{57}Co source; a consistent reading does ensure, however, that the ^{99m}Tc setting is functioning in a consistent manner.)
6. Adjust the radionuclide selector dial to the setting for ^{99}Mo.
7. Repeat the above procedure for a ^{137}Cs source (approximately 100-200 μCi) at the ^{99}Mo calibration settings, again recording the reading in the log book and/or plotting it on a graph. (Note again that the reading of ^{137}Cs at this setting will not yield the correct activity for the ^{137}Cs source; a consistent reading does ensure, however, that the ^{99}Mo setting is functioning consistently.)
8. One of the long-lived sources (e.g., ^{137}Cs) may be used to check all commonly used settings on the calibrator. This is done by placing the source into the calibrator, serially setting the calibrator for each routinely used radionuclide, and recording the results in the log book. A quarterly check is usually sufficient to evaluate other settings. This relative response test should be done quarterly and results evaluated for changes.

The instrument should operate within the specifications for repeatability given in the Operator's Manual. If a reading falls outside the expected range, the background and source readings should be repeated. If a repeated reading again falls outside the expected range, reproducibility of the instrument is suspect. An abnormally high reading may indicate contamination of the source, and a wipe test should be performed. A change in readings on all settings indicates a problem in the overall operation of the instrument, whereas a change in reading at one setting indicates a problem in the nuclide correction circuit, such as an incorrect setting or faulty electrical connection. In either case the laboratory supervisor should be contacted.

Plot of Calibrator Readings

Daily readings obtained with ^{57}Co and ^{137}Cs sources should be recorded and plotted on semi-logarithmic graph paper, with the calibrator reading recorded on the logarithmic scale. A graph of the day-to-day operation will quickly show any changes or trends in readings.

1. Calibrator readings for the two sources must be determined at the initiation of the quality assurance program. These readings should be the average of at least ten readings for each source, obtained at different times during a working day. These averages become the source readings at day zero.

2. Graph the expected reading over a period of time. As shown in Figure 7, 0-10 weeks may be plotted on one cycle of the 2 cycle semi-log graph paper, 10-20 weeks on the other cycle. With the accompanying decay data for ^{57}Co, the activity remaining after 10 and 20 weeks is computed and plotted on the graph at the appropriate dates. A straight line is drawn for each cycle indicating decay of the source over 20 weeks.

3. Repeat step 2 for ^{137}Cs. Although ^{137}Cs does not decay appreciably over 1 year, a decay table is given for this radionuclide and for correction of the small amount of decay during the year.

4. The error of the average calibrator reading is determined by the product of the average reading and the reproducibility error of the individual calibrator as given by the manufacturer. The error (+ and -) should be determined for the average reading. For example, if the calibrator manufacturer states a reproducibility of ± 5 percent, the error is ± (.05) x the average reading. This is determined for the end point of each cycle on the graph. Straight lines are drawn parallel to the decay line, delineating the accepted limits of precision.

5. Daily readings of the check sources should fall within the lines drawn in step 4.

DECAY SCHEDULE

Cobalt 57 — Weeks — Half-life: 270 days

	0	1	2	3	4	5	6	7	8	9
0	-	.982	.965	.948	.931	.914	.898	.882	.866	.851
10	.836	.821	.806	.792	.778	.764	.750	.737	.724	.711
20	.698	.686	.673	.661	.650	.638	.627	.616	.605	.594
30	.583	.573	.563	.553	.543	.533	.524	.514	.505	.496
40	.487	.478	.467	.461	.453	.445	.437	.429	.421	.414
50	.407	.400	.392	.385	.378	.372	.365	.359	.352	.346
60	.339	.333	.327	.322	.316	.310	.305	.299	.294	.289
70	.284	.279	.274	.269	.264	.259	.254	.250	.245	.241
80	.237	.233	.229	.224	.220	.217	.213	.209	.205	.201
90	.198	.194	.191	.187	.184	.181	.178	.174	.171	.168

Cesium 137 — Months — Half-life: 30 years

	0	1	2	3	4	5	6	7	8	9	10	11
0	-	.998	.996	.994	.992	.990	.989	.987	.985	.983	.981	.979
1	.977	.975	.973	.972	.970	.968	.966	.964	.962	.960	.959	.957
2	.955	.953	.951	.949	.948	.946	.944	.942	.940	.938	.937	.935
3	.933	.931	.929	.928	.926	.924	.922	.921	.919	.917	.915	.913
4	.911	.910	.908	.906	.905	.903	.901	.900	.898	.896	.894	.893

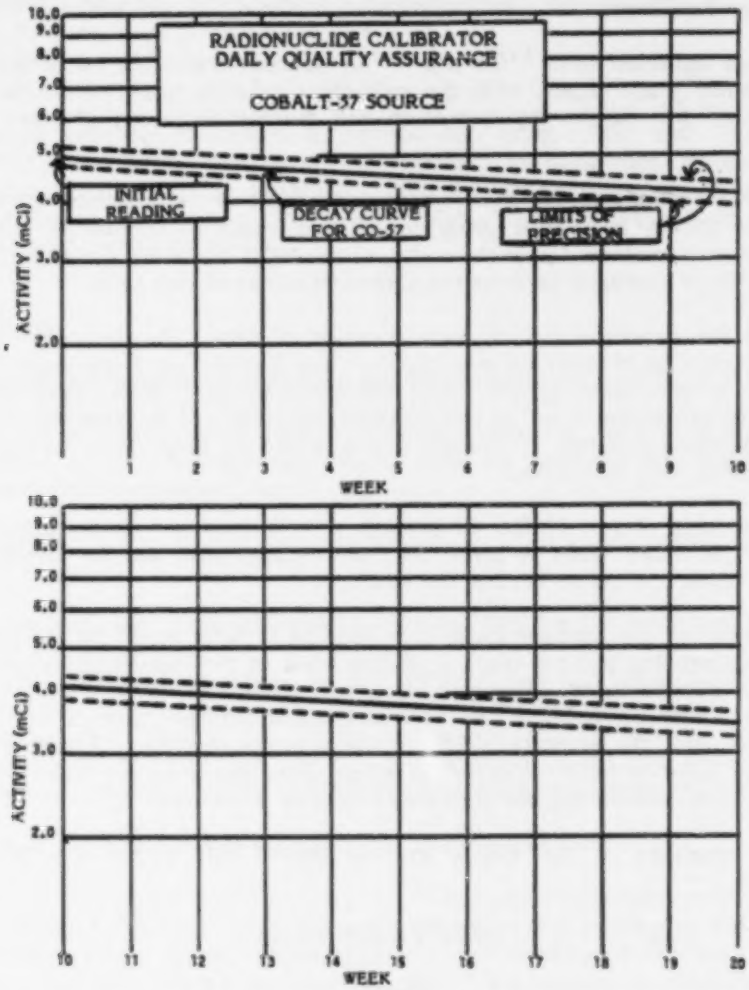

Figure 7. Plot of calibrator readings.

Evaluation of Geometry Response

Volume and position dependence, which may introduce errors in assaying a radioactive sample, may be evaluated by the following tests:

1. Volume dependence:

Materials: Radioactive sample such as ^{131}I or ^{99m}Tc (0.5 cc)
Test tube with cap or 5 cc or 10 cc syringe
Saline
Linear graph paper

Procedure:
1. Transfer a small volume (e.g. 0.5 cc) of the radioactive sample into the test tube or syringe.
2. Assay the sample, taking care to ensure that the radioactive sample is in the same position in the well each time a reading is obtained.
3. Add approximately 0.5 cc of saline to the sample, mix well and assay. Record the total volume, reading, and time.

4. Repeat step 3 until a total volume of 5.0 cc is obtained. If volumes commonly assayed in the calibrator exceed 5.0 cc continue adding saline up to the appropriate volume.

5. Correct all readings for decay of the sample, if necessary.

6. Plot observed reading versus volume. This plot should yield a straight horizontal line if there is no volume dependence.

2. Position dependence:

Materials: Small test tube with cap
String (approximately 0.5 meter)
Metric ruler
Piece of cardboard (10 cm x 10 cm)
Radioactive sample (0.5 cc)

Procedure: 1. Transfer the radioactive sample to the test tube. Cap and tape the top. Attach a string as shown in Figure 8.

2. Make a small hole in the center of the cardboard. The string is passed through this to position the test tube in the center of the well.

3. Place the sample at the bottom of the well. Mark the string at this position (Fig. 9).

4. Take a reading.

5. Raising the test tube, obtain readings at 1 cm intervals. Repeat until 10 or 12 readings have been obtained.

6. Plot the observed activity versus height in the well (Fig. 10).

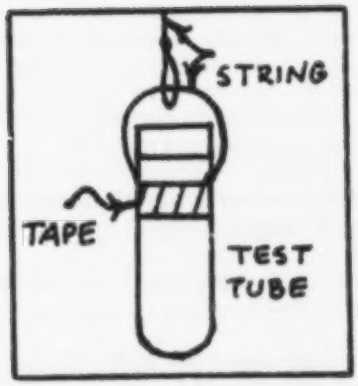

Figure 8. Method for suspending source in radionuclide calibrator well.

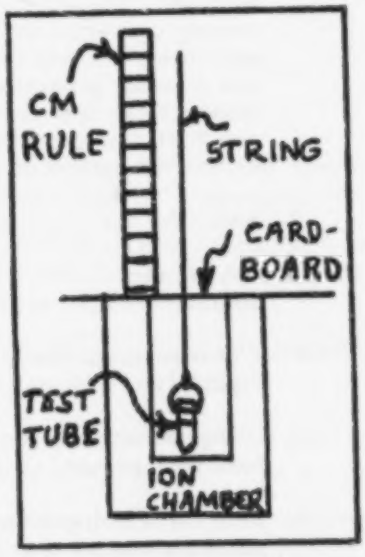

Figure 9. Arrangement of materials for measuring the position dependence of radionuclide calibrators.

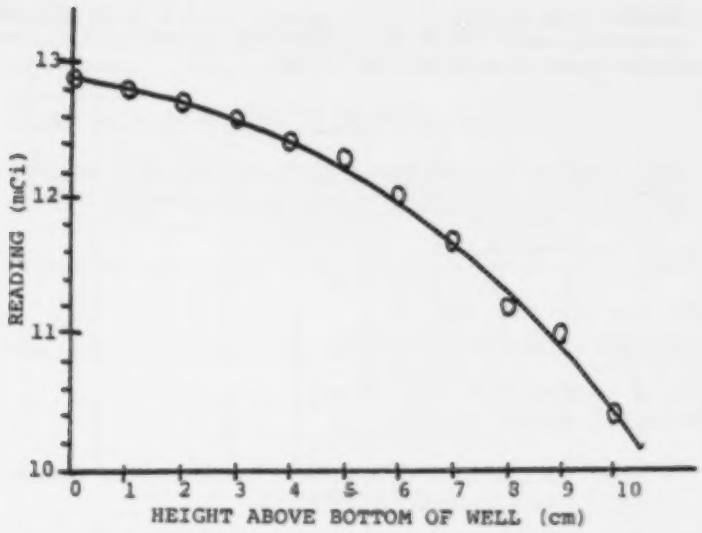

Figure 10. Reading versus height above bottom of well.

Linearity Test of a Radionuclide Calibrator

This test evaluates the response of the calibrator to a range of activities.

Materials:
1. High activity source of ^{99m}Tc comparable to the highest activity assayed in the calibrator.
2. 4-cycle semi-logarithmic graph paper.

Procedure:
1. Obtain a vial of ^{99m}Tc. If the entire vial of ^{99m}Tc eluate is routinely assayed, the test activity should be the eluate on the day the generator is received. The problem arises of obtaining a high activity source while maintaining operation of the department. To minimize disruption of clinical activities, this test could be started on a non-working day, with eluate from the previous generator. If the test is started on a regular working day, the eluate from the previous generator may provide adequate activity for the first few procedures, with later eluate provided by a second elution of the new generator.
2. Assay the vial in the calibrator, recording the time and reading.
3. Repeat step 2 every few hours for approximately 2 days. Data should be obtained that reflect readings on different ranges.
4. Plot observed activity versus time on four cycle semi-log paper, as shown in Figure 11.
5. Using the activity measured at 30 hours, calculate the activity that should have been present at the time of the first measurement.
6. Plot the activity determined in step 5 and draw a straight line between this point and the point at 30 hours.
7. The measured activities should be within ± 5 percent of the decay predicted curve if the calibrator is performing in an acceptable linear manner (6).

8. A shift of the curve in the region of range change (e.g. when going from millicuries to microcuries) indicates a misadjustment of the range selector. The repairman should be notified of this and adjustment should be made using the NRC guide or equivalent methods.

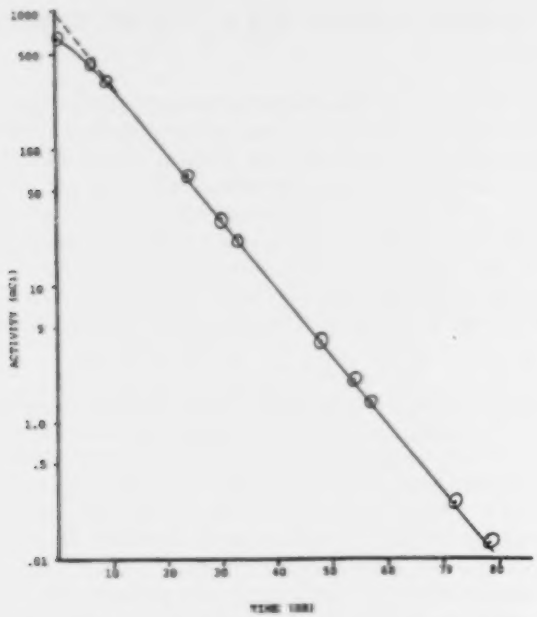

Figure 11. Observed activity versus time.

In the example, the response of the calibrator is nonlinear above approximately 200 mCi. By extrapolating the linear portion of the curve, corrections of observed activity may be made. For example, an observed reading of 350 mCi is a true activity of 400 mCi. No offset in ranges is observed.

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SECTION IV

QUALITY ASSURANCE PROGRAM FOR RADIOPHARMACEUTICALS

A quality assurance program for radiopharmaceuticals includes procedures and tests necessary to ensure the safe and effective use of radioactive products administered to patients. In nuclear medicine, drugs usually are used in subpharmacological dosages (i.e. quantities which do not cause any detectable change in any measurable physiological characteristic of the patient). Hence, from a pharmacologic point of view, nuclear medicine drugs are relatively safe in comparison to other therapeutic or diagnostic drugs which do evoke a pharmacological response. For example, a 100 μCi sample of carrier free ^{123}I contains only 5×10^{-8} mg of iodine; this is less than the quantity of iodine found in a slice of bread. On the other hand, a patient dosage of an iodinated contrast agent may contain 5.2 g of iodine.

The relative pharmacological safety of radiopharmaceuticals and their use primarily for diagnosis, rather than for treatment of disease or relief of pain, have often resulted in the wrong impression that radiopharmaceuticals are not drugs. The status of all radiopharmaceuticals, as repeatedly stated by the Food and Drug Administration, is that they are indeed drugs and therefore are subject to the regulations of the Federal Food, Drug, and Cosmetic Act and the Code of Federal Regulations. These regulations, as well as the infrequent but occasional instances of adverse reactions, are reasons for maintaining a quality assurance program for radiopharmaceuticals. Furthermore, such a program is essential to ensure the effectiveness of any agent in terms of its intended use.

A quality assurance program for radiopharmaceuticals includes tests to ensure that the radiopharmaceutical is sterile, pyrogen-free, of appropriate purity, and contains the correct radionuclide in the correct chemical form and the correct activity for its intended use. In addition, the radiopharmaceutical must be properly labeled, prepared, and stored for use.

STERILITY

Sterility implies the absence of all living microorganisms. Prepared radiopharmaceuticals and radiopharmaceutical kits are guaranteed by the manufacturer to be sterile prior to use. However, the sterility testing performed by a manufacturer is based on statistical sampling of batches of preparations; therefore, the possibility exists that a nonsterile preparation could pass all control procedures. Also, radiopharmaceutical kits could become contaminated during the process of labeling and shipping.

A quality assurance program in the nuclear medicine laboratory should consist of careful aseptic handling of kits, including the appropriate use of sterile equipment and the swabbing of all vials with a disinfectant. When possible, manufacturers include an additional safeguard by adding a preservative to their kits. If microorganisms are introduced into the preparation, the preservative will prevent the microorganisms from multiplying and increasing the extent of contamination.

In addition, samples of radiopharmaceuticals should be tested randomly by sterility testing procedures recommended by the United States Pharmacopeia (1). The two accepted media for sterility testing are fluid thioglycollate medium, which is used mainly for indication of bacterial contamination, and soybean-casein digest, which is useful for detecting low levels of aerobic bacteria and fungi. The use of both media provides a rather complete test of the sterility of a radiopharmaceutical. In the past, Sabourad's broth was used extensively for sterility testing; however, the latest Pharmacopeia has omitted this medium

from its listing. The sterility test takes 7 to 14 days for incubation, so short-lived radiopharmaceuticals often cannot be evaluated prior to use. However, the test is useful to ensure maintenance of sterile technique and particularly for evaluation of products newly introduced in the laboratory.

Radiopharmaceuticals may be tested for sterility after the fact by weekly batch testing. Vials of each radiopharmaceutical are saved and allowed to decay. For each agent, a small volume (e.g., 1 ml) is obtained and batched for testing, often by the hospital chemistry laboratory. If a positive test is obtained, each vial of the agent is retested. Care must be taken to prevent accidental contamination of the needle or vial during batching. Such a testing program can provide insights on the habits and techniques of the staff during preparation and handling of radiopharmaceuticals.

PYROGENICITY

Pyrogens are non-filterable byproducts of bacteria, yeasts, viruses or molds. Pyrogens may produce symptoms of fever, chills, malaise, pain in joints, pallor, apprehension, and substernal oppression. Endotoxins produced by gram-negative bacteria are the most potent pyrogenic substances. However, living organisms need not be present for a preparation to be pyrogenic; hence, sterility does not ensure lack of pyrogens. Pyrogens may be destroyed by autoclaving at 160 °C for 10 hours; however, the most reliable way to ensure freedom from pyrogens is to prevent their introduction into the preparation. This can be done by maintaining strict sterile technique and using pyrogen free solutions and materials in the preparation of radiopharmaceuticals.

The test for pyrogens outlined in the U.S. Pharmacopeia involves the injection of an appropriate volume of the radiopharmaceutical into three mature healthy rabbits weighing not less than 1,500 g each. The rectal temperatures of the rabbits are then observed for 3 hours. The final temperature is compared with the initial, normal temperature. The rise in temperatures may not exceed 0.6 °C for each rabbit, and the sum of the three temperatures may not exceed 1.4 °C. If these limits are exceeded, the test is repeated with five additional rabbits. If not more than three rabbits each exceed 0.6 °C or the sum of the rise in temperature of eight rabbits does not exceed 3.7 °C, the radiopharmaceutical meets the requirements for absence of pyrogens. Due to the expense and difficulty associated with this test, and the infrequent occurrence of positive results, few nuclear medicine laboratories test for pyrogens routinely. In the event that a pyrogen reaction is suspected, the radiopharmaceutical may be allowed to decay and sent to a commercial pyrogen testing laboratory for evaluation.

An alternative test for pyrogens, particularly those endotoxic in nature, uses the lysate from amebocytes of the horseshoe crab (limulus). A positive test is indicated by formation of a solid gel in the product after addition of an aliquot of the radiopharmaceutical (2). This test has not been officially recognized by the U.S. Pharmacopeia for final product testing, although it may be used for in-process testing and in research. Current studies show that the limulus lysate test for pyrogens correlates with the USP rabbit test in more than 99 percent of the tests performed. The limulus lysate test may be valuable for rapid evaluation of a radiopharmaceutical if a pyrogen reaction is suspected, but at the present time may not be used as the official test of the product.

One last item should be discussed in relation to pyrogens. People are many times more sensitive to pyrogens when the drug is administered intrathecally as for a cisternogram. Therefore, special precautions are necessary in the quality assurance of drugs used in cisternography. Each vial of the drug should be used only once. This eliminates the possibility that a previous withdrawal may have contaminated the vial.

PURITY

The purity of a radiopharmaceutical is the percent of the radiopharmaceutical present in the desired chemical, radionuclidic, and radiochemical form. Chemical purity is the portion of the radiopharmaceutical sample which is present in the desired chemical form. High chemical purity of a product is ensured by the use only of raw materials of the highest obtainable chemical purity. Chemical purity is guaranteed by manufacturers of radiopharmaceutical kits and, in general, testing for chemical impurities requires equipment and personnel not found in most nuclear medicine laboratories. Therefore, purchase of kits, prepared radiopharmaceuticals, and generators should be only from approved sources.

Radionuclidic purity is the fraction of the total activity of a sample which is contributed to the radiopharmaceutical by the desired radionuclide. An ideal radiopharmaceutical should contain essentially no radionuclides other than the radionuclide desired. In the production of some radionuclides, it is impossible to obtain a completely pure radionuclide product. In these cases, radionuclidic impurities must be less than the maximum allowable impurity levels set by the U.S. Nuclear Regulatory Commission. Radionuclide impurities may cause an inaccurate activity assay of a radiopharmaceutical. For example, the high energy impurities of ^{123}I (primarily ^{124}I) will greatly affect the assay of this radionuclide. Radionuclidic impurities do not contribute any useful information to a nuclear study, while the patient may receive a higher radiation absorbed dose if impurities are present. This is especially true if the impurity has a long biological half life and localizes in a specific organ.

Packages of prepared radiopharmaceuticals should be randomly checked for radionuclidic impurities which may have been introduced during preparation, particularly when a radiopharmaceutical is first obtained from a different manufacturer. A probe with a single channel analyzer may be used to check for radionuclidic contaminants. A knowledge of potential contaminants will allow a quick check at the appropriate energies to determine whether the radionuclidic contaminant is present. If available, a multichannel analyzer with a sodium iodide (NaI(Tl)) or germanium lithium (Ge(Li)) detector is useful for quickly determining the presence and identity of radionuclidic impurities. If the system is calibrated for a range of energies a quantitative determination of the activity of the radionuclidic impurities may also be made.

Radiochemical purity is the fraction of the total sample activity which is present in the desired chemical form. For example, ^{131}I sodium iodate in a solution of ^{131}I sodium iodide constitutes a radiochemical impurity. In prepared kits, essentially all of the radioactivity should be in the form of the tagged radiopharmaceutical. With kit radiopharmaceuticals, poor studies are often the result of radiochemical impurities. For example, in ^{99m}Tc kits, ^{99m}Tc pertechnetate and "reduced hydrolyzed technetium" are radiochemical impurities. A poor tag in commercially available ^{99m}Tc kits may often be related to the use of stannous (Sn^{+2}) ion as a reducing agent in the kits. To act as a reducing agent, tin must be present in the Sn^{+2} form. The ease of air oxidation of Sn^{+2} to Sn^{+4} results in a decrease in the amount of Sn^{+2} present in the kit, thus preventing adequate reduction of pertechnetate. Storage of kits at reduced temperature may minimize this problem and increase their shelf life. If free ^{99m}Tc pertechnetate is observed repeatedly, possible sources of trouble may be insufficient amounts of Sn^{+2} present in the kit for reliable and complete labeling, the possibility that the Sn^{+2} was oxidized during preparation or storage, or the chance that insufficient stannous ion is present for the generator eluate used. Changes to consider include using an alternative kit with more stannous ion present, minimizing injection of air into the vial during preparation, switching to a different generator, or using two smaller generators per week instead of one high activity generator. High activity generators have been considered a possible source of increased tagging problems. If breakdown is occurring throughout the day, storage in the refrigerator may slow this process.

The presence and quantity of radiochemical impurities may be determined by chromatographic techniques, such as thin-layer chromatography or "instant thin-layer

chroma-chromatography" (ITLC). With these techniques, radiochemical impurities may be separated from the tagged radiopharmaceutical by placing a drop of the radiopharmaceutical approximately 1 cm from the bottom of a strip of chromatographic paper or ITLC media (Fig. 12). About one-half of a drop that will hang on a 25-gauge needle is reasonable for spotting. The strip is then placed upright in a suitable holder containing a small amount of an appropriate solvent.

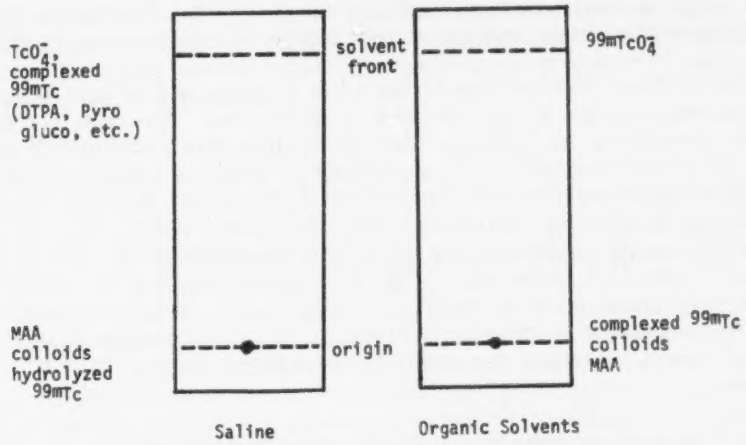

Figure 12. Chromatographic strip spotted for development; location of solvent front following development.

The solvent migrates up the strip by absorption and capillary action. The radiopharmaceutical and radiochemical impurities tend to move at different rates within the solvent, thus separating the components. When the solvent front reaches the top of the strip, the strip is removed and allowed to dry. The origin and solvent front are marked for reference in counting the strip.

A number of solvents may be used to separate the radiochemical impurities from the radiopharmaceutical, including saline, acetone and methyl ethyl ketone (MEK). The migration characteristics of ^{99m}Tc radiopharmaceuticals are shown in Table 3. Free pertechnetate may be separated from sulfur colloid, macroaggregated albumin (MAA) and microspheres using an organic solvent such as acetone or MEK. Complexed radiopharmaceuticals such as bone agents, glucoheptonate and DTPA may contain both "reduced hydrolyzed technetium" and pertechnetate as radiochemical impurities. To determine the relative activity of each impurity, two radiochromatographic strips may be run, one with saline and the other with an organic solvent. The complexed agent and pertechnetate will migrate to the solvent front in saline, while only the free pertechnetate will migrate in the organic solvent. The reliability of the solvents may be checked by running standards such as pertechnetate. The standard should be observed on the chromatographic strip at the location indicated in Figure 12.

Table 3. Migration characteristics of certain ^{99m}Tc radiopharmaceuticals

1. Pertechnetate	Migrates in acetone, MEK, saline and H_2O.
2. Glucoheptonate DTPA All bone agents	Stationary in organic solvents(acetone, MEK, Migrates in saline, H_2O
3. Colloid, MAA, microspheres	Stationary in all solvents

A number of methods may be used to evaluate the radiochromatographic strips. Since the components of the radiopharmaceutical tend to stay either at the origin or migrate to the solvent front, the strip may be quickly evaluated by counting each end for 1 minute in a

reproducible geometry over a well counter. This is particularly useful for evaluating high activity samples. Also, measurement may be made the following day by cutting the strip into sections and counting each in a test tube with a well counter. A visual inspection of the proportions of activity at the solvent front and origin may be made with a scintillation camera. The radiochromatographic strip may also be evaluated by a scanning device in which the strip is scanned by a radiation detector, with the output of the detector displayed as a function of time (Fig. 13). The area under the peaks is compared to determine the percent tag.

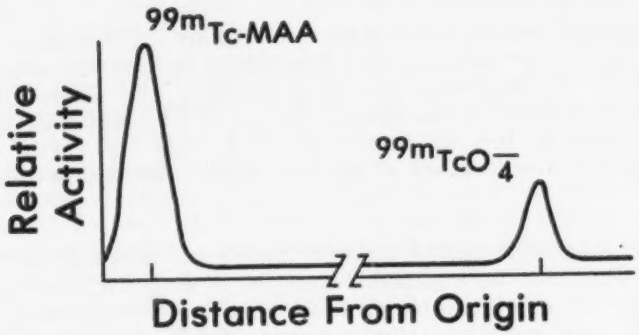

Figure 13. Typical chromatograph scan.

The percent of the radiochemical impurity in the radiopharmaceutical is calculated from the counts observed at the origin and solvent front. Percent free pertechnetate, developed with an organic solvent, is calculated by:

$$\text{percent } ^{99m}TcO_4^- = \frac{\text{Count (solvent front)}}{\text{Count (solvent front)} + \text{Count (origin)}} \times 100$$

The percent of reduced hydrolyzed technetium, with saline as the solvent is calculated by:

$$\text{percent reduced hydrolyzed technetium} = \frac{\text{Count (origin)}}{\text{Count (origin)} + \text{Count (solvent front)}} \times 100$$

percent bound = 100 - (percent free $^{99m}TcO_4^-$ + percent hydrolyzed ^{99m}Tc).

Tagging efficiencies of greater than 95 percent are often obtained. Radiopharmaceuticals with a tagging efficiency less than 90 percent should not be used. Limits of acceptability should be established by observing tagging efficiencies and clinical results.

The location of the radiochemical impurities may not be as distinct as shown in Figure 12. For example, with bone agents, 2-10 percent of the activity of the radiopharmaceutical may remain at the origin and 5-10 percent in the middle of the strip. Although it has been shown that it is difficult to correlate radiochromatographic results with clinical results, the normal radiochromatographic pattern may be established by evaluating clinical results for good bone uptake. The normal pattern should be established for each agent and deviations from the normal are an indication for concern.

The frequency that radiopharmaceuticals should be tested by radiochromatography has not been established. Testing for radiochemical impurities should be performed on a routine basis when evaluating a new kit. If a history of high tagging efficiency is observed, the radiopharmaceutical may be tested on a random basis thereafter. Whenever any clinical scan shows abnormal thyroid, stomach or liver uptake the radiopharmaceutical should be chromatographed immediately to develop correlations between in vitro assays and in vivo behavior.

All radiopharmaceutical kits should be used according to manufacturer's instructions. They must be stored at the correct temperature. The amount of radioactivity added to the kit must not exceed that recommended by the manufacturer and the kit must be reconstituted before the expiration date. The labeled radiopharmaceutical must be dispensed within the period of time recommended by the manufacturer or determined in the laboratory. For example, a poor study obtained late in the day could be caused by dissociation of the pharmaceutical from the ^{99m}Tc, producing a large percent of pertechnetate in the administered dosage. Repeat radiochromatographic testing throughout the day may be used to establish the length of time over which the radiopharmaceutical has high radiochemical purity.

Radiopharmaceuticals also should be examined visually (using appropriate radiation safety techniques) to determine whether any particulate matter, cloudiness, or off-color is present in the sample. For example, aluminum ion in ^{99m}Tc eluate may cause a visually apparent flocculant precipitate in the preparation of ^{99m}Tc sulfur colloid. Other particulate contaminants, such as bits of rubber stoppers, may also be in the vial. A quick inspection can determine the presence of foreign material and aid in establishing the safety of the preparation.

Technetium-99m macroaggregated albumin (MAA) and microspheres should be checked for particle size. This may be evaluated easily with a microscope and hemacytometer. Under the microscope a hemacytometer grid looks like the drawing shown in Figure 14. The depth is a uniform 0.1 mm and the smallest squares are 50 µm (1/20 mm) on a side.

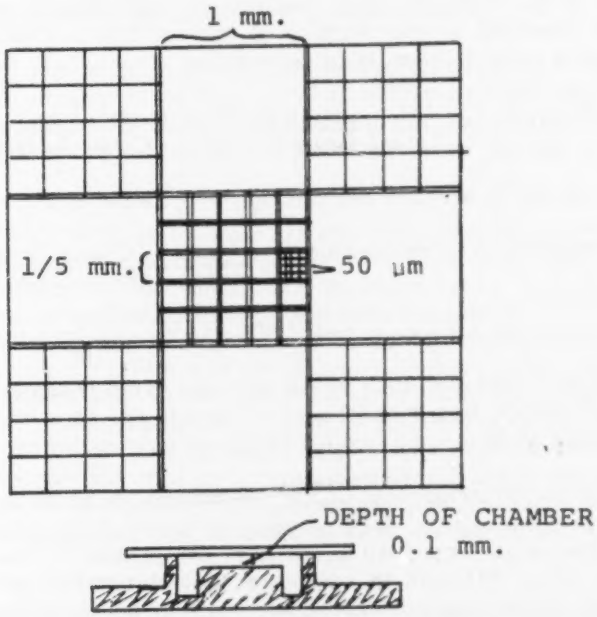

Figure 14. Diagram of hemacytometer grids used for particle sizing

By measuring the length of a particle against the 50 µm divisions, the size distribution of particles may be determined. At least 90 percent of MAA particles should measure from 10-90 µm with no particles greater than 150 µm. If lung uptake is observed when using sulfur colloid, the size of the colloid particles should be checked to determine whether in vivo behavior is a result of the size of the particles in the agent.

The number of particles in the MAA may be determined simultaneously. By counting the number of particles in the entire 3 mm square and dividing by 0.0009, the original number of particles per cc of solution is approximated. This is an important consideration when dealing with MAA or microsphere particles, especially with children and infants, since only as many capillaries as needed for the study should be blocked for a statistically significant study (about 30,000 for an adult).

Additional aspects of a radiopharmaceutical quality assurance program include procedures to ensure that the patient is administered the appropriate amount of the correct radiopharmaceutical. All vials must be correctly labeled and stored in a way that will minimize the possibility of administering the incorrect radiopharmaceutical. Many nuclear medicine laboratories have found a color coding of vials and vial shields very effective. If a number of dosages are drawn at one time, the syringes may also be color coded with labels identifying the agent, date, and activity of the sample. The volume of radiopharmaceutical needed must be calculated accurately. Additionally, the dosage must be assayed prior to injection to ensure that it contains the correct amount of activity. Occasionally the tagged radiopharmaceutical will be adsorbed on the walls of the vial, producing a lower specific activity than calculated. This problem is revealed by assaying the syringe post injection. Accurate records must be kept of the use of the radiopharmaceutical including identification of the patients and activity administered. Prior to injection, each patient must be properly identified and should be informed of the procedure. Patient consent forms must be obtained for all investigational new drugs (IND). The radiopharmaceutical is then administered in the prescribed fashion.

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SECTION V

HANDLING OF RADIOACTIVE XENON

Radioactive xenon (^{133}Xe) is used as a gas or dissolved in saline to evaluate pulmonary function. Xenon-133 is a noble gas with a half-life of 5.27 days that is obtained from the fission of uranium. The penetrating emissions of interest are the 81-keV gamma rays emitted during 37 percent of all decays. Other emissions include a 346-keV beta particle and a number of characteristic x rays with an average energy of 31 keV. Xenon gas is heavier than air and is slightly soluble in saline. All of these characteristics make ^{133}Xe useful for pulmonary studies, but also present unique problems in storage, administration to the patient, and disposal.

STORING AND HANDLING

Xenon-133 is commercially available as a gas in three types of containers. The simplest container to use is the unit dose container; however, this method is also the most expensive per mCi. With the unit dose container, storage and handling are minimized since the gas may be stored as received, preferably in a well ventilated area. The gas is dispensed with a special administration device provided by the manufacturer, shown in Figure 15. The second system available for ^{133}Xe is as a compressed gas mixed with normal air in activities from 100 to 1,000 mCi and concentrations from 2 to 10 mCi/ml of gas. This approach may prove less expensive than the unit dose container if more than five or so xenon studies are performed weekly.

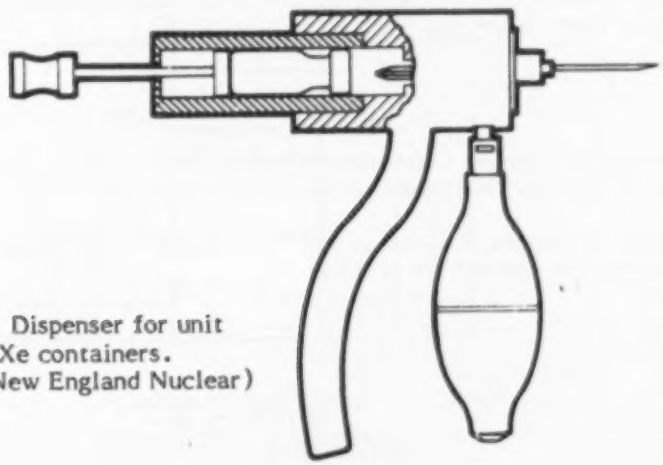

Figure 15. Dispenser for unit dose ^{133}Xe containers. (Courtesy of New England Nuclear)

A third commercially available form of ^{133}Xe is a 10 cc glass ampule containing 1 Ci ^{133}Xe under reduced pressure. This is the most inexpensive way of obtaining Xe per mCi. The method is advantageous if a large number of studies are performed each week. The ^{133}Xe is dispensed in the laboratory with a commercially available storage and transfer device such as that shown in Figure 16. The apparatus breaks the glass ampule safely and allows the ^{133}Xe to equilibrate with some volume of normal air, usually 100 cc. A filter in the apparatus traps glass fragments and other particulate matter. The desired volume of Xe is dispensed into a syringe as needed.

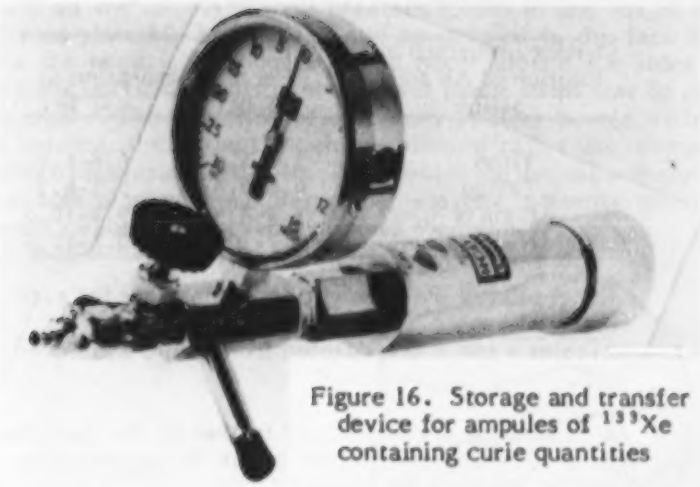

Figure 16. Storage and transfer device for ampules of ^{133}Xe containing curie quantities

With any of these handling methods, losses of ^{133}Xe from the dispensing unit are inevitable, and the unit should be stored in a ventilated hood. Because Xe is highly soluble in oils and greases, it is important to avoid lubricated stopcocks or fittings during preparation and dispensing. Another potential source of loss may be adsorption of the gas on plastic syringes (Table 4), and it is recommended that the dosage be drawn just prior to administration. Xenon gas also can be lost when removing the syringe from the dispenser. Therefore, upon removing the syringe, it should be capped immediately. Speed is important in this operation to prevent a portion of the gas from escaping into the room.

*Table 4. Adsorption of ^{133}Xe in plastic syringes

Time in syringe	Percent Adsorption of ^{133}Xe	
	Saline	Gas
5 min.	5-8	-
40 min.	17-19	2-3
110 min	25-28	-
6 hr.	-	7-10
7 hr.	45-51	-
22 hr.	50-55	9-11

*Tables 4 and 5 are adapted from Ponto and Loken (1).

Radioactive Xe dissolved in saline also presents a number of problems in handling and storage. To obtain ^{133}Xe in saline, curie amounts of Xe in a glass ampule may be dissolved in saline in a commercially available transfer and storage vessel. Individual dosages are drawn from this vessel into a syringe as needed. Adsorption of the Xe on O-ring fittings in the transfer vessel may occur, as shown in Table 5. The data presented are "worst case" examples in which the O-rings were immersed in the Xe saline solution, but imply that adsorption may cause a significant loss of radioactive Xe during normal storage and handling. These data indicate that the activity to be administered should be drawn into the syringe just prior to administration. Alternately, the dosage may be drawn into a glass syringe, since glass adsorbs less than 1 percent of the gas under all conditions (1). Xenon-133 dissolved in saline may also be obtained in unit dose vials. Losses due to adsorption by the rubber or plastic components of vials may be checked by assaying the vial after the Xe has been removed.

*Table 5. Adsorption of ^{133}Xe from Xe-saline solutions on plastics and rubbers.

O-Ring immersed in solution of Xe and saline	Percent adsorption at 18 hr.	32 hr.
Viton	5.0-5.8	6.6-8.4
Teflon	4.6-5.6	5.1-6.3
Buna N	8.2-8.9	9.8-10.3
Neoprene	9.7-10.4	10.8-12.0

Ranges listed are for eight determinations for each material.

*Tables 4 and 5 are adapted from Ponto and Loken (1).

Handling of ^{133}Xe in solution is complicated further by the fact that it is only slightly soluble in saline, with a solubility coefficient about 20 percent that of carbon dioxide. Xenon in solution should be refrigerated, since it is more soluble in cold liquids. To prevent loss of Xe from solution, the solution should not be exposed to air. Exposure to air may be a significant problem when Xe in solution is transferred into a syringe, because much or essentially all of the Xe may be contained in air bubbles which may be present.

HANDLING OF RADIOACTIVE XENON FOR PATIENT STUDIES

In ventilation studies, 10-15 mCi of ^{133}Xe are administered to the patient for imaging. The assay of the activity of the administered sample in a radionuclide calibrator is affected greatly by the geometry of the container used to hold the Xe, because its 81 keV photons are attenuated readily. Large differences in assay readings are noted among plastic syringes and various types of glass containers. The accuracy of assay depends upon the method used to calibrate the radionuclide calibrator for ^{133}Xe, and the type of container subsequently used to assay the gas. Xenon-133 standards in glass ampules are available from the National Bureau of Standards. In general, the assay of ^{133}Xe is one of the more difficult applications of the radionuclide calibrator (2).

A common procedure for ventilation studies involves administration of a bolus of ^{133}Xe during a single deep inspiration which is held for 15-20 seconds. Administration is followed by an equilibrium phase of 3-5 minutes during which the patient breathes a mixture of Xe and oxygen in a closed system. During the subsequent washout phase, the patient inhales room air, and the expired air containing Xe is collected for disposal. The biological half-life (the time for clearance of half the Xe from the patient's system) is only a few minutes for most normal patients.

For perfusion of the lungs, a 10-15 mCi dose of ^{133}Xe dissolved in saline may be injected intravenously. During the first passage of the injected radionuclide through the lungs, 95 percent of the Xe is cleared from the bloodstream into the alveolar space. The activity then is distributed according to the relative volume of the patient's lungs and rebreathing system. The equilibrium phase and washout may be evaluated as described above.

During a ventilation study, a major cause of radioactive contamination is the patient's misunderstanding of his/her role in the procedure. Clear and adequate instructions are necessary prior to the administration of Xe so that the patient understands what he/she is to do. The patient must remain attached to the breathing system until the entire study is completed. Leakage of Xe from around the patient's mouth has been found to be a major source of contamination during ventilation studies. Some laboratories use mouthpieces and noseclips for the procedure. Many patients tend to leak air around the mouthpiece, and

some patients may attempt to spit the mouthpiece out entirely during the procedure. To prevent this occurrence, a face mask which covers both the mouth and the nose may be used (Fig. 17), and all the air the patient breathes moves in and out of the mask only. The mask should fit comfortably but tightly, and be secured to the face by means of a rubber strap around the head. No leakage should occur around the sides of the mask. In the event that a tight seal is difficult to obtain, wet gauze strips may be placed between the cheeks and the mask. This situation often occurs in older people with sunken cheek flesh. With either method, the patient should be allowed to breathe through the system for a few moments before administering the Xe. This enables the patient to become accustomed to the "feel" of the breathing system. Remember - a few moments taken for adequate instruction can prevent radioactive contamination of the room.

Figure 17. Breathing mask used in ventilation studies.

Xenon Breathing Systems

There are three major types of breathing systems currently used for Xe ventilation studies. One type incorporates a respirometer within a fully automated system, as shown in Figure 18. This type of system usually is designed for use with a mouthpiece and noseclip, but can be adapted for use with a face mask. Many of these units use internal blowers to flush the system at the end of the study to guarantee that no residual ^{133}Xe remains. Automated respirometer systems are useful when more sophisticated pulmonary function maneuvers are desired in conjunction with the ventilation study. Manufacturers of these units specify that they are shielded for technologist safety.

Partially automated xenon breathing systems are also commercially available. A shielded unit contains the valve assembly for directing the flow of ^{133}Xe during the three phases of the study, and the rebreathing and collection container to which oxygen may be added as necessary. Xenon breathing systems may also be constructed in-house with a spirometer. These systems allow additional pulmonary function information to be obtained in conjunction with the xenon ventilation study. However, care must be taken to ensure tight seals of all connections to prevent leakage.

One way to overcome the cost of respirometer systems is to construct a breathing system in the laboratory as shown in Figure 19. During use of this system, the actual diffusion of ^{133}Xe through the rubber bag is insignificant because of its short residence time, but buildup of ^{133}Xe in the bag may limit its longevity. Nonpermeable plastic bags can also be used. There are several disposable breathing systems now available commercially (Fig. 20). They are more costly than a reusable system, but they have the advantage of eliminating bacterial transfer from patient to patient.

Figure 18. Fully automated respiratory device.
(Courtesy of RADX)

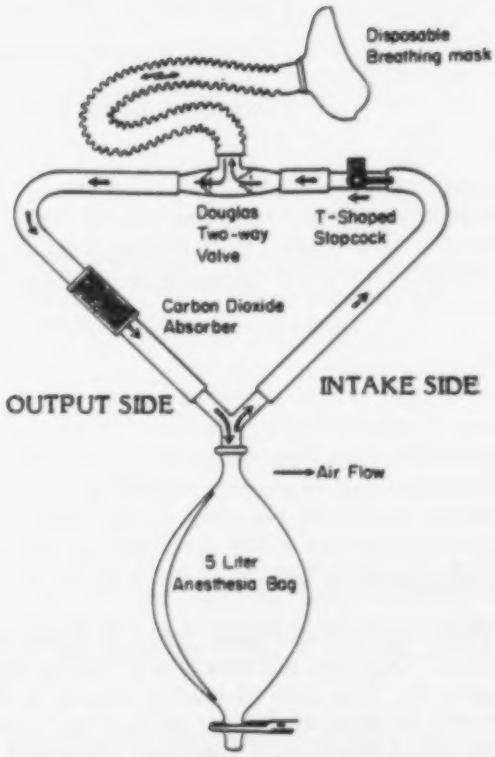

Figure 19. Reusable breathing system constructed "in-house."

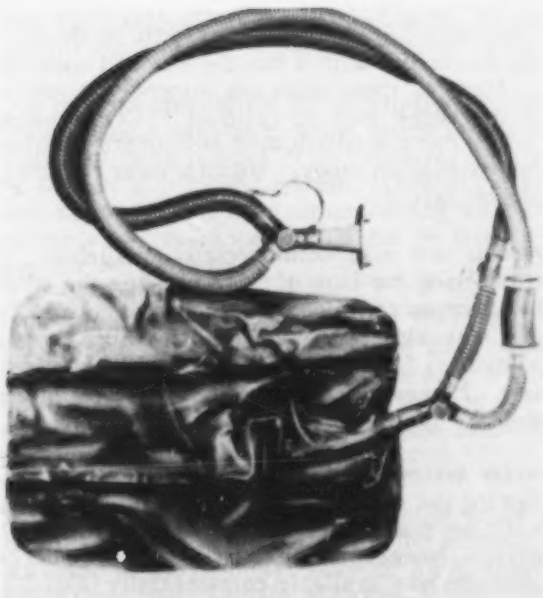

Figure 20. Disposable breathing system.
(Courtesy of Atomic Products Corporation)

These systems can be used with a face mask attached by a short flexible plastic tube to the storage bag. The system is made of nonpermeable plastic and incorporates a 12 liter bag which can be used for both rebreathing and collection. By initially filling the bag half full, (i.e., with 5-6 liters of oxygen) it is possible to obtain an adequate concentration of ^{133}Xe for imaging by administering 10-15 mCi of Xe as a gas. Some systems incorporate an inlet for administration. However, the inlet port is not really useful for gas administration because the diameter of the port allows some radioactive gas to escape before the port can be closed. It is also possible to inject through the flexible plastic tube immediately before the face mask. The plastic is self-sealing after withdrawal of the needle, and no radioactive gas should escape through the injection site.

Unlike the automated systems, the reusable and disposable systems are unshielded. Studies of potential radiation hazards to individuals using these systems reveal that a technologist could receive a whole body exposure of 1 mR if involved in ten ^{133}Xe procedures per month (3). This exposure is rather low compared to other nuclear medicine procedures. To further reduce personnel exposures, a shielded area for the rebreathing and collection bag can be constructed if desired.

The system utilized for delivery of ^{133}Xe to patients varies from one department to the next, depending on the specific needs of the department. With any system, however, care must be taken to prevent radioactive contamination by careful and thoughtful instructions to the patient, and proper use of the equipment.

Collection and Disposal of Radioactive Xenon

There are a number of methods of collecting and disposing of ^{133}Xe during patient washout. The simplest method uses a balloon or bag attached to or incorporated in the breathing system. With the disposable Xe administration system, the rebreathing bag can also be used for collection. The reusable administration system requires that an additional balloon be attached for washout, as illustrated in Figure 21. When washout is completed, the collected radioactive gas is expelled into a vented hood.

It is also possible to construct an exhaust system to vent to the outside all air expired during washout. The construction involves assembling a blower motor and an exhaust system constructed from flexible dryer ducting. During washout, the duct is held at the breathing system outlet, and the motor draws expired air to the outside. This type of system has been used satisfactorily in a number of laboratories for many years.

Both of the methods which dispose of Xe through a hood require adequate dilution of the gas before release to the atmosphere. The location of the outlet for both the hood and the duct mentioned above should follow normal placement requirements. The final concentration of ^{133}Xe at the exhaust must be less than the maximum permissible concentration (MPC) of ^{133}Xe in a nonoccupationally exposed area. Sample calculations for determining concentration at the exhaust are given at the end of this section. In some cases where the number of studies is very large, or an exhaust hood or adequate dilution is not available, it is necessary to collect and contain the exhaled gas.

One method of containing Xe is storage of the exhaled gas (Fig. 22). The gas is collected in a balloon or similar holding bag. The patient's breathing apparatus is then disconnected and the radioactive contents of the bag pumped under pressure into a storage gas tank. The xenon gas is stored until it has decayed to essentially background level, and then released to the atmosphere. Two tanks, rotated to allow for decay, are usually necessary. This method yields very low radiation levels to personnel.

Another method of containing the Xe utilizes an activated charcoal gas trap. Such traps are commercially available and are designed to adsorb ^{133}Xe from the exhaust flow (Fig. 23). During washout, a piece of flexible tubing connects the breathing system outlet to the inlet of the gas trap. Exhaust air is drawn by a vacuum pump through a dessicant such as

Drierite or silica gel to remove moisture, followed by a charcoal filter cartridge to adsorb the ^{133}Xe. Commercial traps are adequately shielded to reduce the radiation level. A simple, inexpensive method for constructing a trap has been described in the literature (4).

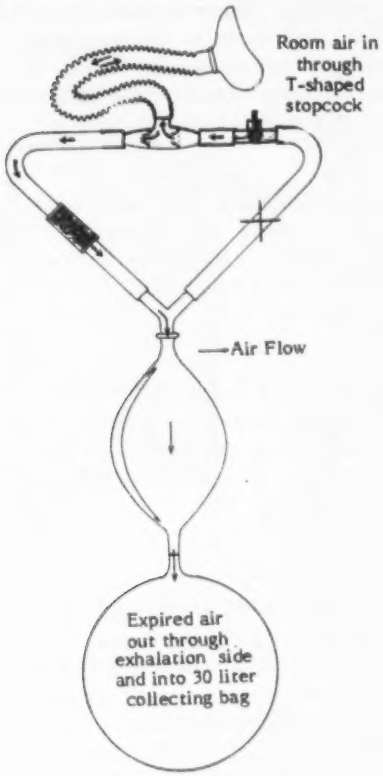

Figure 21. Additional collection bag for reusable system.

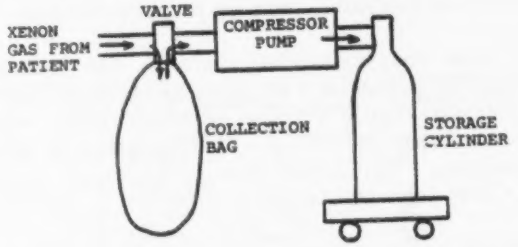

Figure 22. Diagram of tank for storage of ^{133}Xe.

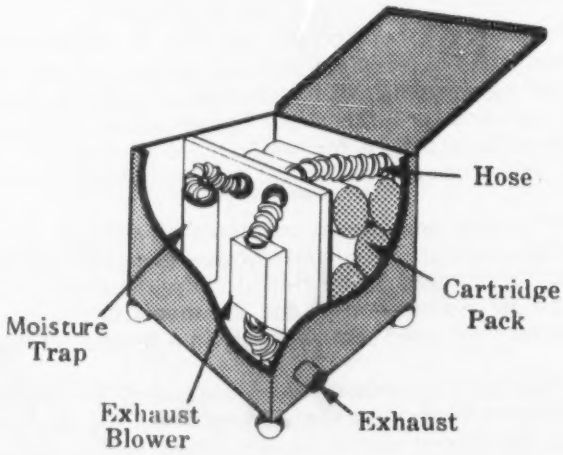

Figure 23. Commercially available charcoal trap (Courtesy of Nuclear Associates, Inc.)

Replacement of activated charcoal traps will depend on usage. Adsorption of Xe to charcoal is due mainly to very weak forces (5). With continued flow through the trap, the Xe will migrate in the direction of the flow. In addition, charcoal will adsorb a variety of airborne materials besides Xe. The life of the charcoal trap is affected by a number of variables, including flow rate, geometry of the trap, humidity, temperature, air pollution, type of activated charcoal, and concentration of Xe in the air. As a result, the exhaust port of the trap must be monitored frequently. To do this, an air sample using a test tube may be obtained at the exhaust port of the trap. This is counted in a well counter and compared with a background air sample obtained prior to the study. A reading of more than two times background indicates leakage of ^{133}Xe through the charcoal trap. Another method of monitoring the exhaust port is to fill a 5 liter polyethylene bag at the exhaust port. The bag is sealed and counted in front of a scintillation camera. The count rate is recorded in a log book and compared with previous readings (6).

The desiccant that removes moisture from the exhaled Xe gas must also be checked. Most desiccants are available with a color indicator which indicates when the desiccant must be replaced. The desiccant may be reused by drying in an oven at approximately 120 °C. The length of time necessary for drying may be determined by repeatedly weighing a small amount of the desiccant until no weight loss is observed between two weighings.

An additional problem with the use of charcoal traps relates to the rate of air flow. Charcoal traps are most efficient with an air flow of 5 liters per minute. However, most people breathe at a rate of 15 liters per minute. To prevent pressure buildup that would make breathing difficult for the patient, it is recommended that exhaled air be collected in a bag or other expandable interface, then pumped through the charcoal at its optimum flow rate.

Patient Absorbed Dose

The absorbed dose to the patient from a ^{133}Xe ventilation study has been evaluated by a number of investigators (7,8,9). Data in Table 6 are based on the assumption that the patient was administered 15 mCi of ^{133}Xe which was rebreathed for 4 minutes. Actual patient absorbed dose is dependent on the protocol used for ventilation studies and the washout time of Xe, which is often longer than in normal patients. As can be seen from the table, the radiation hazard to the patient is very low because of the short biological half-life of ^{133}Xe.

Table 6. Patient dose after administration of 15 mCi ^{133}Xe

	Inhalation	Intravenous
Lungs	147 mrad	166 mrad
Fat	97 mrad	76 mrad
Blood	7 mrad	6.8 mrad

Potential Radioactive Contamination and Occupational Hazards

The potential of ^{133}Xe for radioactive contamination and resulting hazards to personnel have been examined by a number of investigators (10,11). A major concern is the potential for buildup of concentrations of ^{133}Xe gas that exceed the maximum permissible concentration (MPC) of 1.0×10^{-5} μCi/cm^3. Under normal conditions for direct exhaust of Xe through a hood or for activated charcoal trapping, the MPC is occasionally exceeded for occupationally exposed individuals. This event often results from an incident such as leakage around the patient's mouth, coughing during the study, or problems arising during pumping of the exhaled gas into the trap or hood, including backup and leakage of the gas because of a kink in the flexible duct or use of too high a flow rate. One study (8) has shown that the ^{133}Xe quickly disperses throughout the entire department. Although contamination levels may be below the MPC, this level of ^{133}Xe contamination may affect the background count rate of well counters used at low energy settings such as those for ^{125}I. Since Xe is heavier than air, the flow in the imaging room should be monitored periodically with a GM survey meter to check for buildup of Xe due to adsorption in the floor wax. Problems arising from the use of Xe for ventilation procedures usually can be prevented. Proper equipment and its careful utilization, together with adequate patient instructions and an awareness of correct radionuclide handling techniques, will protect the patient, technologist, and department from the potential hazards of ^{133}Xe.

CALCULATIONS FOR DISPOSAL OF XENON-133 BY DILUTION IN A HOOD

Before ^{133}Xe gas can be disposed of by dilution in air through a hood, it is necessary to calculate the dilution rate. First determine the amount of Xe that will be dispersed and the flow rate. Also make sure the hood vents directly to the roof without interconnection to other hoods in the hospital, so that the gas will not be drawn back into occupied rooms at some other point in the building. Also check for presence of intake ducts on roof or upper levels of the building.

The following is a sample calculation for finding the maximum allowable ^{133}Xe that can be disposed of per week using the dilution method.

Sample Calculation

Xenon-133 used in a nuclear medicine department is recovered in a storage device and released through an exhaust hood to a discharge point on the roof of the building. The hood vents directly to the roof. The capacity of the hood is 1036 cubic feet per minute. What is the maximum permissible weekly discharge rate?

With the assumption that the hood operates continuously, the flow rate of air through the hood is:

$$1036 \frac{ft^3}{min} \times 28{,}320 \frac{cc}{ft^3} \times \frac{60\ min}{hr} \times \frac{168\ hr}{wk} = 3 \times 10^{11} \frac{cc}{wk}$$

The maximum permissible concentration of ^{133}Xe in the air is 3×10^{-7} $\mu Ci/cc$ in unrestricted areas (Code of Federal Regulations, Title 10, Part 20.103, Appendix B, Table 1).

With the assumption that there is no additional dilution of the ^{133}Xe in the atmosphere, the maximum permissible discharge is thus:

$$3 \times 10^{11} \frac{cc}{wk} \times 3 \times 10^{-7} \frac{\mu Ci}{cc} = 9 \times 10^{4}\ \mu Ci = 90\ mCi/wk.$$

For control purposes, the maximum weekly discharge is 90 mCi. In practice it is recommended that the routine weekly discharge be set lower than the MPC. Then the facility has a reserve in the event of an unplanned radio-xenon release.

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SECTION VI

RADIATION SAFETY IN NUCLEAR MEDICINE

Safe handling of radioactive materials in the nuclear medicine laboratory must be the constant concern of all nuclear medicine personnel. Major procedures involved in safe handling include:

A. Exposure control by use of the principles of time, distance, and shielding;

B. Contamination control by use of preventive procedures, confinement of potential contamination, and effective decontamination techniques; and

C. Periodic surveillance to monitor exposure and contamination control.

EXPOSURE CONTROL

Reduction of radiation exposure to personnel and patients in the nuclear medicine laboratory is accomplished by the judicious use of the principles of time, distance, and shielding. The goal of exposure control is to reduce exposure to levels as low as reasonably achievable (ALARA) (1) while maintaining a working environment in which tasks may be performed quickly and efficiently.

The easiest way to reduce exposure is to minimize the time spent in a radiation area. For example, when a new procedure is introduced where high activity sources must be handled, "cold" runs of the procedure will help ensure that it is performed quickly yet correctly. Another way to minimize the time any one person is exposed to high levels of radiation is to rotate the duties of nuclear medicine personnel.

Radiation exposure is inversely proportional to the square of the distance to the radiation source (inverse square law). For example, by increasing the distance by a factor of two, the exposure is decreased by a factor of four. Although this reduction in exposure is exactly true only for a point source, the use of distance, especially in handling radioactive sources, will greatly reduce exposure. When transferring an unshielded radioactive vial, for example, the use of tongs or similar remote handling devices will reduce exposure significantly, particularly to the hands.

In some cases the only way of reducing exposure is by shielding the radiation source. Shielding involves positioning a suitable material between the source and the area where the exposure is measured (i.e. where personnel will be located). This material is usually lead in the form of bricks, sheets, or various shaped lead glass containers.

The thickness of shielding material necessary to reduce the exposure by half is called the half-value layer (HVL). The HVL is a function of the energy of the radiation and the material used for shielding and the beam geometry. For example, the HVL of lead for ^{99m}Tc (140 keV photons) is 0.31 mm, while for ^{131}I (364 keV photons) the HVL is 2.3 mm. The HVL of concrete for ^{99m}Tc is 19.3 mm. The total thickness of shielding material necessary to reduce the radiation intensity to an acceptable level depends on the activity that must be shielded (e.g. a ^{131}I eluate vial containing 100 mCi will require more shielding than a 3 mCi sample of ^{131}I). The amount of shielding used should be sufficient to reduce exposure levels as low as reasonably acheivable.

In many nuclear medicine laboratories the ^{99}Mo - ^{99m}Tc generator and ^{99m}Tc eluate present the highest levels of radioactivity which must be shielded. The generator itself is shielded for shipping, and most manufacturers provide additional shields in which the generator should be stored. Additional shielding may be constructed around the generator with lead bricks. The configuration of the bricks should be sturdy and provide no continuous gaps. When viewed from above, the configuration of bricks shown in Figure 24 (a) is preferable to that shown in Figure 24 (b).

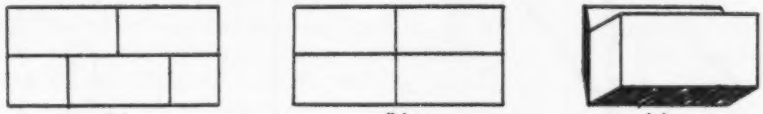

Figure 24. Lead brick configurations

The seam lines are not continuous and there is less possibility of radiation leakage. The seam lines may also be soldered. The wedge shaped lead bricks shown in Figure 24 (c) provide sturdy and gap-free construction. Shielding must also be provided behind and below the generator, again with lead brick or lead sheets. The ^{99m}Tc eluate, which often exceeds a few hundred mCi, must be shielded at all times in a vial shield usually provided by the generator manufacturer, or in a heavier shield provided by the laboratory.

The area used for preparation of radiopharmaceuticals and dispensing of patient doses requires special shielding. Visibility of the working area must be provided, but the eyes and whole body should be shielded. There is a hazard of serious exposure of the eyes from an unshielded source (Table 7). Many laboratories provide protection with an L-block shield in which lead glass is used to provide visibility of the working area (Fig. 25). With an L-block, the sides and rear of the working area are not shielded, allowing possible exposure of other personnel working in the area. To provide more complete shielding, a working area may be constructed as shown in Figure 26. The area is shielded, with lead brick and a sheet of lead glass placed at eye level. Three slots are provided at the front which allow access to the working area while ensuring whole body shielding.

Table 7. Eye exposure rates from various radionuclides

Radionuclide	mR/hr-mCi at 15 cm
Technetium-99m	3.1
Iodine-131	9.7
Xenon-133	3.1
Molybdenum-99	5.7
Mercury-203	5.3
Selenium-75	7.7
Ytterbium-169	4.0

In addition to shielding the working area, all vials and syringes should be shielded to further reduce exposure to the hands. Vial holders are preferred that allow only the rubber portion of the vial to be exposed while a dosage is withdrawn, since these holders minimize exposure. These vials may be made from lead, lead glass, or lead glass and steel. The vial shields should be clearly marked to prevent accidental use of the wrong vial. If a large number of radiopharmaceuticals are used, a vial shield color coding system should be used. Shielded vials may be stored at the rear of the working area, and may be additionally shielded by placing them behind a row of lead bricks.

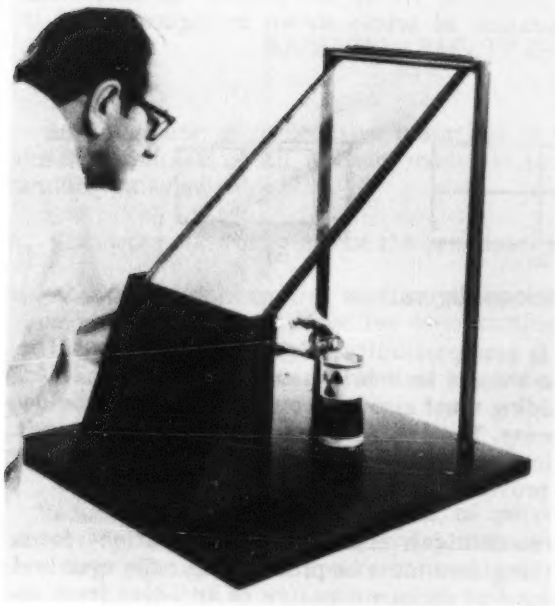

Figure 25. L-Block shielding
(Courtesy Nuclear Associates, Inc.)

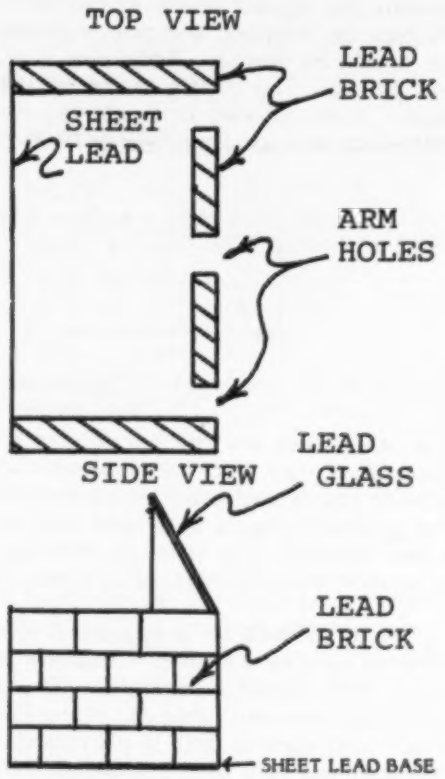

Figure 26. Diagram of shielded working area for preparation, storage and dispensing of radiopharmaceuticals.

Filled syringes to be used for patient injections should be shielded during transport and, if practical, during injection. Holders may be used for individual syringes. If a large number of syringes are to be transported at one time, a shielded carrying tray may be used. A tray may provide the safest method of transportation if the hot lab is located a distance from the area where patients will be injected.

Syringe Shields

Injecting the radiopharmaceutical into a patient often represents the largest single source of radiation exposure to personnel. Estimates of 1.6 to 2 mrem to the index finger of the hand per mCi ^{99m}Tc injected have been calculated. Syringe shields can reduce radiation exposures by a factor of 50 to 80 percent when used in the preparation of radiopharmaceuticals and in patient injections (2). The use of a syringe shield is required by the Nuclear Regulatory Commission (3). Some people find that shields prevent the necessary "feel" during penetration of the tissue and vein. However, many of the newer, light-weight shields are relatively easy to use. Many physicians and technologists find the shields for 3 cc syringes usable in most situations. Often no difficulty is encountered if the technologist or physician is taught initially to inject using shielded syringes. Most syringe shields have small lead glass windows for viewing the radioactive sample; however, difficulty may be encountered when trying to read a volume scale accurately.

Most shields for 1 cc slip-lock tuberculin syringes should not be used, since the syringe must be taken apart to place it in the shield and again to remove it from the shield for assay

in the radionuclide calibrator. Such dismantling introduces contamination and sterility problems. Shields available for 1 cc Luer-lock tuberculin syringes eliminate the need to disassemble the syringe and therefore are more advantageous to use.

A number of different syringe shields are available commercially. Commonly, shields are designed for use with a specific size syringe (Figure 27). They are made of a tube of lead with a lead glass insert for viewing the radioactive sample. Recently, other designs have been introduced. One* is a strip of covered lead foil that wraps around the syringe, providing a compact light-weight shield useful for low activity samples of ^{99m}Tc. A light weight tantalum shield was developed by the National Institutes of Health. This shield is designed to retract while the dosage is assayed in the radionuclide calibrator, thereby reducing exposure to the technologist during handling (Figure 28). Another shield** is a high density lead glass barrel designed for use with available specific size syringes. This design provides greater visibility for drawing and injecting radiopharmaceuticals (Figure 29).

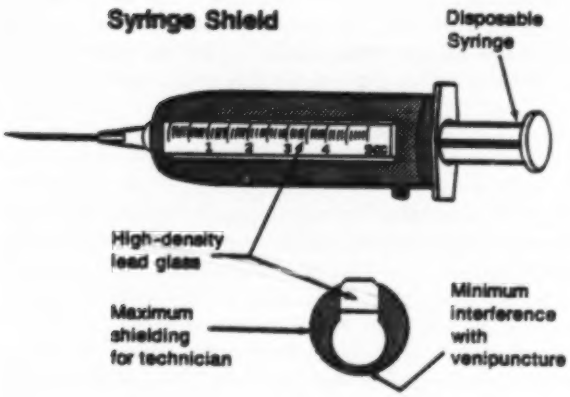

Figure 27. Standard commercially available syringe shield.
(Courtesy of Nuclear Associates, Inc.)

Figure 28. Retractable tantalum syringe shield developed by the National Institutes of Health.

Figure 29. Shield with high density lead glass barrel.
(Courtesy of Nuclear Pacific, Inc.)

*"Roll-Your-Own", Atomic Development Corporation.
**Nuclear Pacific, Incorporated.

EXPOSURE FROM PATIENTS

Patients who have been injected with radioactive materials also represent a source of potential exposure of personnel to radiation. For example, at the University of Colorado Medical Center, the exposure rate from a patient administered 20 mCi of ^{99m}Tc-DTPA for a brain scan was 5-8 mR/hr at one foot and 1-2 mR/hr at three feet from the patient. Use of a lead apron (0.5 mm lead) to drape the trunk of the patient reduces this exposure to less than 0.5 mR/hr. This procedure does not interfere with the study or inconvenience the patient. Although use of a lead apron is not appropriate in many situations, it may be used effectively with brain scans to provide additional reduction in the exposure of personnel to radiation. The technologist should also wear a lead apron and should make every effort to remain as far from the patient as reasonable during the study.

SHIELDING OF RADIOACTIVE WASTE

All radioactive vials, used syringes and potentially contaminated materials (e.g., gloves, cotton swabs, and absorbent paper) must be stored immediately after use and prior to disposal. The storage area should be shielded and located in a locked area away from the flow of traffic in the department; often a corner of the hot lab may be used. A bin of lead bricks lined with plastic garbage bags is adequate. The bin may contain receptacles for separation of vials, syringes, needles, and such items as contaminated gloves, swabs, and paper.

PERSONNEL MONITORING

The effectiveness of radiation control must be continually monitored. Recommendations regarding the maximum dose that occupationally exposed personnel may receive have been made by various advisory committees, including the National Council on Radiation Protection and Measurements (NCRP). Many of the recommendations of NCRP Report No. 39 have been adopted and are being enforced by the U.S. Nuclear Regulatory Commission (NRC) and State regulatory agencies. The occupational dose limits from external radiation exposure are described in terms of the total dose to specific portions of the body that may be accumulated over the period of one year (Table 8). These limits should not be viewed as a "permitted" dose, however, since the basis of radiation safety practices is to make the dose to personnel "as low as reasonably achievable."

Table 8. Maximum permissible dose equivalent for occupational exposure (NCRP)

	Per Year
Whole body	5 rems
Skin	15 rems
Hands	75 rems
Forearms	30 rems
Gonads, lens, red bone marrow	5 rems
All other organs	15 rems

Occupationally exposed personnel usually wear lightweight film badges on the trunk of the body to monitor accumulated external whole body doses. A film badge consists of one or more small sheets of photographic film enclosed in a plastic packet. Most badges include metallic filters which attenuate the radiation to varying degrees, enabling estimates of the type and energy of the radiation to which the wearer was exposed. The film is changed routinely, usually monthly, and developed. The developed film may be compared with film exposed to known amounts of radiation to estimate the accumulated whole body dose. Advantages of film dosimetry include a permanent record of the individual's dose, an approximate determination of radiation energy, and relatively low cost. Disadvantages include temperature, pressure, and light sensitivity, the bulkiness of the film badge for extremity

monitoring, and the time delay between exposure and knowledge of the exposure. Many institutions prefer the use of personnel monitoring devices which employ thermoluminescent dosimeters (TLD) in addition to or in place of film. A TLD dosimeter may be a chip, rod, or or small sealed packet of powder of a thermoluminescent material such as lithium fluoride. Upon exposure to ionizing radiation, electrons in the crystalline structure are excited to higher energy states where some are "trapped." Upon heating, the electrons are returned to ground state, and the excitation energy appears in the form of light. The heating, detection, and measurement of the amount of light released is accomplished with a TLD reader that includes a photomultiplier tube and associated electronics. A reading is obtained that is proportional to the amount of energy absorbed by the TLD. Advantages of the TLD include size, and re-use of the powder, rod, or chip. A disadvantage is lack of a permanent record.

With nuclear medicine procedures the highest dose will usually be to the hands, especially the fingertips. This exposure will not be reflected in whole body film badge readings. Hence, the hands should also be monitored to ensure that the MPD of 75 rems per year is not exceeded. Exposure to the index finger from 20 mCi of ^{99m}Tc may be 22 R/hr from an unshielded syringe and 300 mR/hr from a shielded syringe, representing the highest exposure to the hands (4). A TLD in the form of a ring badge is often used for this purpose. Often both TLD ring badges, preferably worn on the index finger, and film whole body badges are used by nuclear medicine personnel to provide a relatively complete record of exposure.

Doses recorded by TLD and film badges are reported to the supervisor of the nuclear medicine department. Regulations require that these reports be made available to the personnel involved. These individuals should review their own reports. Exposure monitoring provides an indication of the effectiveness of exposure control methods. High readings indicate that methods being employed are inadequate, and steps should be taken to reduce exposure to personnel. Very often, changing one or two techniques will lower the exposure considerably.

A portable ionization chamber survey meter may also be used for measuring exposure rates. Ionization chambers are instruments in which the ions produced by radiation in a gas-filled chamber are collected at electrodes to produce an electrical current. The current is amplified to a measurable level and registered on a rate meter marked in units of exposure rate. A portable ionization chamber is basically energy independent, but if the instrument is kept calibrated, it will provide correct readings of exposure for the range of energies found in nuclear medicine, with the possible exception of very low energy photons such as those from ^{125}I. Portable chambers are lightweight, rugged, simple in construction, and reliable if properly cared for. Most portable ionization chambers have a selector switch with positions for various ranges of exposure rates and a battery check. To properly operate the chamber, it should be allowed to warm up for a few mintues before use and the battery should be checked according to manufacturer's instructions. Since most rate meters have a slow time response, sufficient dime must be allowed for the meter to stabilize before obtaining a reading.

Potential exposures in various areas of a nuclear medicine department should be monitored routinely. An ionization chamber with a response as low as a few tenths of a mR may be used for this purpose. The survey includes determination of the radiation exposure level in various imaging rooms, hallways and areas of the hot lab. The hot lab is the most critical room and all areas of potential exposure should be evaluated, including in front of the dosage preparation area under normal conditions, and in front of the waste storage area. Readings should be obtained at the usual working distance from the sources of radiation. The exposure at eye level should also be evaluated. Readings may be recorded on a chart or diagram of the areas to be evaluated and compared with previous exposure levels. When high readings are noted, the source of exposure should be determined and corrective action (e.g., additional shielding) taken.

CONTAMINATION CONTROL

With the transfer of large amounts of radioactive materials in the nuclear medicine laboratory, there exists the potential for radioactive contamination. This is a serious problem from the aspects of potential external and internal exposure of personnel and contamination of equipment. A number of general procedures should be followed whenever working with unsealed sources of radioactive materials. Knee length lab coats should always be worn and checked regularly, especially if contamination is suspected. When handling radioactive material containers, gloves should be worn, preferably latex surgical gloves, since they are less permeable to contamination. Gloves should be changed after each operation and disposed in a contaminated waste receptacle to prevent cross contamination. Also, gloves must be removed before touching objects such as a pencil or telephone receiver or when using the radionuclide calibrator. All working surfaces should be covered with plastic lined absorbent paper. In the event of a spill, the paper will prevent the spread of radioactive liquid and may be easily removed as radioactive waste. Plastic lined absorbent paper may be obtained in rolls, or disposable diapers may be used. Diapers are especially convenient for lining trays and carts used to transport materials for injection. The absorbent paper should be changed often and always following a spill.

A Geiger-Muller (GM) survey meter should be used for detecting radioactive contamination that emits gamma rays and/or high energy beta particles. A GM tube is a gas-filled detector in which the potential difference between the electrodes is high enough that a primary ionization event produces an avalanche of ionization of the counting gas. This amplification of the ionization produces large pulses that are constant in size and independent of the type of radiation producing the primary ionization. GM detectors are more sensitive than ionization chambers, but their response is dependent upon the type and energy of the radiation and the orientation of the detector. Hence, they should be used as only a rough guide to exposure levels, and then only if carefully calibrated with sources of clinical interest. The sensitivity and ease of use of the GM detector make it excellent for detection of radioactivity. Stationary GM detectors may be used to monitor the level of radiation in a room such as the hot lab. Portable GM survey meters are useful for detecting areas of radioactive contamination. Both may have an audio signal that will indicate the relative level of radiation detected. The probe containing the GM tube of the detector often has a window which may be unshielded or shielded. When the window is unshielded, high energy betas may be detected which are attenuated when the window is shielded. This will permit some differentiation between gamma and beta emitters.

Potential causes of contamination within the department should be identified and appropriate preventive measures taken. All cotton swabs used in maintaining sterile technique must be handled as possibly contaminated, including those used during dosage preparation and patient injection. Small receptacles near working areas may be used to hold such contaminated waste until transfer is made to the departmental waste storage area. Patients who have received ^{99m}Tc and ^{131}I also present a potential source of contamination, since the saliva and mucous secretions contain radioactivity which may contaminate other objects in the room. Care should be taken to cover surfaces that the patient may touch, (e.g. camera collimator) with a disposable material such as a plastic wrap. A critical contamination problem is the care of ^{131}I therapy patients. Procedures for care of these patients should be available in every department where ^{131}I therapy is performed. Satisfactory procedures are described in NCRP Report No. 37.

RECEIPT OF RADIOACTIVE MATERIAL

Proper control of radioactive material requires that upon receipt, a radioactive package is checked to ensure that it is not damaged or contaminated either by the shipper or the manufacturer. The shipping carton and inner package must be visually inspected for evidence of damage or leakage. If damage or leakage is found, wipe tests of the outer and inner package containing the radioactive material will alert laboratory personnel of potential contamination and allow preventive measures before widespread laboratory

contamination has occurred. In addition the NRC now requires that recipients of packages containing appreciable quantities of radioactive material must monitor the external surface for contamination (5). The packages must be monitored as soon as practicable, within three hours if received during normal working hours, and in any case within 18 hours. The term "appreciable quantity" means liquid sources of greater than 1 mCi with a 30-day half-life or those greater than 100 mCi in activity.

Contamination survey requirements may be satisfied with a simple wipe of the package with a moistened paper towel over an area equal to or greater than 100 cm^2. The wipe is then checked for activity with an end window GM counter or a well counter. Removable external contamination in excess of 0.01 microcuries (22,000 dpm) must be reported to the final carrier involved, and to the NRC or local State radiological health organization. To accurately determine this level of activity, the GM survey meter or well counter must be calibrated with appropriate standards. In addition, measures should be taken to prevent further spread of contamination.

Although not required, it is suggested that all radioactive materials received at the laboratory should be checked for contamination of the external and internal package and assayed to ensure that the received product is actually that indicated on the label.

DISPOSAL

Methods used for disposal of radioactive materials must minimize potential exposure to the general public. For this reason, minimal amounts of radioactive materials may be released to the environment, but records must be kept documenting the method of disposal and the quantity of radioactivity released. Disposal of byproduct radioactive waste is governed by NRC regulations 10 CFR 20. Routes of disposal are:

(1) Release to an authorized recipient.

(2) Release to the sanitary sewer, taking into account solubility, quantity and concentration levels.

(3) Burial in soil at "designated" sites (may require special permit).

(4) Incineration (may require special permit).

(5) Decay to negligible levels of activity (exempt).

A record of disposal is required regardless of the disposal method used. This record should include the activity of the source and the method of disposal.

Many of the radionuclides such as ^{99m}Tc used in nuclear medicine may be disposed of by allowing them to decay to "exempt quantities." The quantities of various radionuclides that are exempt are described in 10 CFR 20. One rule of thumb often stated is to allow a source to decay ten half-lives. However, high activity sources will not be below "exempt quantities" in ten half-lives, and the actual time necessary to reach an exempt level should be calculated. All radiation warning labels must be removed or obliterated before the containers are allowed to enter normal disposal channels.

It is advisable to use a GM instrument (window open) with an audible monitor to survey all waste released to normal waste disposal channels to ensure that negligible radioactive material is in the containers. Any container with a measurement greater than background should be retained until the level falls below that limit.

A REVIEW OF GOOD LABORATORY PRACTICES

Even with the best controls, contamination will occur occasionally. The laboratory environment and personnel should be surveyed routinely for radioactive contamination. Personnel should check hands and clothes with a GM monitor upon completion of duties involving the handling of radioactive materials, and always before leaving the department. The lab should be surveyed on a routine basis and whenever contamination is suspected. A portable GM survey meter may be used to check surfaces such as counters and floors. In areas of high background, such as near the generator, surfaces may be checked for removable contamination by wiping the area with a damp paper towel or filter paper, and the wipes checked with a GM survey meter. Alternately, a number of wipes may be taken and counted with a NaI(Tl) scintillation detector such as a well counter. Use of a detector with an energy discriminator also allows semi-quantitative determination of the radionuclides that may be the contaminants. In general, any area giving counts higher than two times background should be decontaminated. Laboratories in which ^{3}H or ^{14}C are used require the use of a liquid scintillation detector to count the wipe test for removable contamination. These radionuclides emit only low energy beta particles that will not be detected by a GM survey meter.

If removable radioactivity is found, decontamination procedures should be implemented immediately. Hands and body may often be decontaminated by washing with an appropriate detergent and mild scrubbing. Surface contamination usually may be removed by scrubbing with a detergent or abrasive cleanser. In decontamination procedures, it is important to use only a small amount of liquid to prevent the spread of contamination. A more extensive discussion of decontamination procedures follows.

DECONTAMINATION PROCEDURES

Radioactive accidents and contamination of working areas and personnel occasionally occur in the nuclear medicine laboratory. Identification of potential problems and subsequent corrective measures will help prevent such accidents. In the event of a radioactive accident, decontamination techniques are needed that will minimize exposure to personnel and prevent contamination of other areas of the lab, particularly radiation detection equipment.

Before a radiation accident occurs, decontamination procedures such as those given below must be developed. All personnel should be familiar with the procedures. An occasional "cold" run of decontamination procedures will help ensure immediate implementation in the event of an accident. A package containing supplies for decontamination procedures should be easily accessible in each lab using radioactive materials. This package should include the following materials:

1. Detergent and scouring powder for cleansing
2. Generous supply of paper towels for absorbing waste liquid
3. Plastic backed absorbent paper such as Chux for absorbing liquid waste and covering clean areas
4. Radioactive warning tape and signs for isolating the area
5. Plastic bags, both large and small, for containing waste, and serving as shoe covers
6. Generous supply of disposable latex gloves and small plastic bags to cover hands and survey instruments and disposable smocks, jump suits, and caps for personnel involved in decontamination procedures

7. Scrub brushes for scrubbing the contaminated lab areas and skin

8. Scissors

9. Marking pen to label waste containers

10. Masking tape for sealing bags

11. Filter paper for wipe tests during and following decontamination

Survey instruments either should be available in the area, or the nearest location of survey instruments should be posted.

PROCEDURE FOR A MAJOR RADIOACTIVE ACCIDENT

A major accident in the nuclear medicine laboratory will probably be a liquid radioactive material spill. A satisfactory procedure to follow is:

1. Contain the spill with absorbent paper, shut off ventilation fans, vacate the area and prevent reentrance.

2. Immediately notify the lab supervisor and radiation safety officer. If personally contaminated, either have someone else perform the notification while you proceed with personnel decontamination procedures, or remove contaminated clothing, cover hands with gloves if contamination is suspected and proceed with notification. Every effort must be made to prevent spread of contamination.

3. Survey all persons who may be contaminated. Proceed with personnel decontamination procedure. Do not allow anyone to leave the area until it has been determined that they are not contaminated.

4. Estimate the exposure level. With high exposure levels, more than one occupational worker may need to be enlisted to aid with the initial decontamination procedure, thus limiting the amount of exposure to any one individual. This should be done under the supervision of the lab supervisor or radiation safety officer.

5. Using protective clothing, footwear, and gloves, start decontamination procedures. Work from the outside of the spill toward the center to prevent spreading the spill over a larger area. Working quickly yet carefully, absorb all liquid and place in a plastic bag. Tape bag shut and place in another bag to prevent further contamination. Tape the second bag, label, and store in a shielded area. This procedure will remove much of the radioactivity, allowing the decontamination to proceed at a slower, more deliberate pace. One person should remain uncontaminated to transfer waste as needed and to operate survey instruments.

Area Decontamination - Low Level Exposure

The following applies after contaminated personnel and the major contamination have been confined and removed as outlined in the 5 points above.

1. With a GM survey meter, or using wipes of areas with suspected contamination, define the border of the contaminated area with tape. Cover the surrounding clean area to help prevent accidental tracking of contamination. Start at the outside of the contaminated area and clean toward the center, using detergent and small amounts of liquid. Absorb contaminated liquid with paper towels and place in a marked waste bag. Abrasive powder and a scrub brush may be used to remove persistent contamination. Care should be taken not to splatter the

material by use of the brush. Contaminated wax on tiles may be removed with a strong wax remover. Check frequently with a GM survey meter to determine when an area is below twice background. If another person is not available to help with surveying, remember to change gloves before operating the survey meter. A disposable glove placed over the GM tube will help prevent accidental contamination.

2. When the entire area is thought to be decontaminated, survey thoroughly by obtaining wipes and checking these with the GM survey meter or well counter. If no contamination above twice background is present, remove masking tape and place in waste.

3. Survey protective clothing and place in storage or waste if contaminated. Check for personal contamination and proceed with personal decontamination procedures if necessary.

4. Remove all contaminated waste to the waste storage area.

5. Develop ways in which a repeat of the incident may be prevented.

Some contamination may not be reduced to twice background by cleaning procedures, and other methods may be required. Tile may be removed and replaced. Since most radioactive accidents in the nuclear medicine lab involve radionuclides with a short half-life, areas of persistent low-level contamination may be covered with paper or plastic and lead sheet as necessary, and the radioactive contamination allowed to decay. These areas must be labeled and checked with a GM survey meter after an appropriate time has elapsed.

PERSONNEL DECONTAMINATION

All persons who may have been contaminated during a spill or area decontamination procedure must be checked for contamination before leaving the area. A GM survey meter may be used for this purpose.

1. Check clothing and belongings for contamination. Remove contaminated articles and determine the extent of skin contamination.

2. Local areas of skin contamination may be decontaminated by spot cleaning. Adjacent areas of uncontaminated skin may be covered with plastic and taped to prevent spread of contamination. Wash the skin thoroughly with soap or mild detergent and tepid water, scrubbing gently with a soft brush and rinsing frequently.

3. If skin contamination is extensive, a thorough shower is necessary. Clean hair, hands and fingernails carefully. Cut contaminated hair and fingernails if necessary.

4. If residual contamination exists, remove by further spot cleaning, using the following methods. Avoid prolonged use of any one method. Repeated ineffective decontamination techniques may only irritate the skin, hampering further techniques and increasing absorption of radioactivity through the skin.

   A. Increasingly strong preparations, to be used with water.

      (1) Soap

      (2) Abrasive soap

      (3) Commercial detergents

(4) Chelating agent

(5) Complexing agent (e.g. 1 percent citric acid) should be applied under medical supervision because of potential injury to skin surface.

B. Increasingly strong preparations, to be used without water.

(1) Cornmeal and powdered detergent in equal parts, applied as a paste and gently scrubbed on skin surface. Remove the paste with paper tissue.

(2) Strong cleansing hand cream gently scrubbed on skin surface and removed with paper tissue.

(3) Cream of 4 percent Carbose, 3 percent Versene, 8 percent commercial detergent, and water, gently scrubbed on skin surface and rinsed thoroughly.

C. Persistent contamination may also be removed by perspiration. Wrap the area in plastic or rubber or cover with gloves. Tape securely. After one or two hours remove carefully to prevent recontamination (e.g., turn gloves inside out).

Following skin decontamination procedures, apply lanolin-based creams to offset local irritations.

SUMMARY OF GOOD WORKING HABITS

Good working habits will help ensure both control of exposure and contamination. The following general rules should be observed at all times.

DO: Wear lab coats and impermeable gloves when working with radioactive materials.

Store radioactive materials in a shielded area lined with absorbent paper.

Transport radioactive materials on trays lined with absorbent paper with an impermeable base.

Keep radioactive materials in closed, shielded containers.

Clearly label all radioactive materials.

Perform all new procedures in a "cold run."

Monitor hands, clothing, and all work areas routinely.

Clean up spills promptly, and report serious spills to the radiation safety officer.

Review safety regulations frequently.

Form and maintain good habits.

DO NOT: Pipette by mouth.

Eat, drink, smoke, or apply cosmetics in radioactive material storage or work areas.

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